FULL STUDY PROTOCOL

AN OBSERVATIONAL POST-AUTHORIZATION SAFETY SPECIALIST COHORT EVENT MONITORING STUDY (SCEM) TO MONITOR THE SAFETY AND UTILIZATION OF RIVAROXABAN (XARELTO®) FOR THE PREVENTION OF STROKE IN PATIENTS WITH AF, TREATMENT OF DVT AND PE, AND THE PREVENTION OF RECURRENT DVT AND PE IN THE SECONDARY CARE HOSPITAL SETTING IN ENGLAND AND WALES

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Glossary of terms

Abbreviation	Term
A & E	Accident and Emergency
ADR	Adverse Drug Reaction
ACS	Acute coronary syndrome
AE	Adverse Event
AF	Atrial fibrillation
ALT	alanine aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	aspartate aminotransferase
BMA	British Medical Association
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack
CHM	Commission on Human Medicines
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CYP2CP	Cytochrome P450 2C9
CYP P450	Cytochrome P-450
DMP	Data Management Plan
DSRU	Drug Safety Research Unit
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EMA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drugs Administration
FDR	False Discovery Rate
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GP	General Practitioner
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HLT	Higher Level Term
ID	Incidence Density
INR	International normalized ratio
IRAS	Integrated Research Application System
ISTH	International Society on Thrombosis and Haemostasis
IQR	Interquartile Range
LFT	Liver Function Test
LLT	Lower Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
M-PEM	Modified Prescription-Event Monitoring
NDA	New Drug Application

NHS	National Health Service
NHSRxS	National Health Service Prescription Services
NICE	National Institute for Health and Clinical Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OTC	Over-The-Counter
PCI	Percutaneous coronary insert
PE	Pulmonary embolism
PEM	Prescription Event Monitoring
PIP	Paediatric Investigation Plan
PS	Propensity Scores
PSC	Project Steering Committee
RCT	Randomised Controlled Trial
RAIDAR	Rare and Iatrogenic Adverse Reactions
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SCEM	Specialist Cohort Event Monitoring
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAF	Stroke Prevention in Atrial Fibrillation
SPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
VKA	Vitamin K Antagonist
VKORC1	Vitamin K epoxide reductase complex subunit 1
VTE	Venous thromboembolism

EXECUTIVE SUMMARY

Rivaroxaban, a highly selective direct factor Xa inhibitor which inhibits thrombin formation and the development of thrombi, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacements.[1] On 19 December 2011, the European Commission approved the use of Xarelto in the indications prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) [2] A further variation of marketing authorisation for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults' was approved on 20 November 2012 [3] More recently, a marketing application has been approved in the EU for rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.[4] A Risk Management Plan (RMP) has been developed for rivaroxaban by the manufacturer. This plan includes tools designed to monitor the important risks (including class effects and off-label use). [5]

This postmarketing safety study of rivaroxaban (XARELTO®) is to be carried out by the Drug Safety Research Unit (DSRU) as part of a broader Post-Authorisation Commitment requested by the Committee for Medicinal Products for Human Use (CHMP) to further investigate the safety profile of rivaroxaban in clinical practice. This study, which is designed to monitor the safety profile and drug utilisation of rivaroxaban as prescribed by specialist Healthcare Professionals (HCP) for medical indications requiring anticoagulation (i.e. not the licensed surgical indications for prevention of VTE in adult patients undergoing elective major hip or knee replacement surgery) and used in the secondary care hospital setting in England and Wales, is one of two complementary studies conducted by the DSRU. The other, based in primary care, is a Modified Prescription-Event Monitoring (PEM) Study, the aim of which is to proactively capture safety profile and drug utilisation data in the post-marketing phase of license approval of rivaroxaban as prescribed to patients by general practitioners (GP) in England.

The aim of this Specialist Cohort Event Monitoring (SCEM) study is to monitor the short-term (up to 12 weeks) safety profile and drug utilisation of rivaroxaban as prescribed to patients for medical conditions requiring anticoagulation by specialist HCPs in the secondary care hospital setting in England and Wales. A registry-based observational, population based cohort study with a contextual cohort, utilising the technique of cohort-event-monitoring will be used (section 4) for this purpose. In the three-year post approval period, the study aims to collect exposure and outcome data for a cohort of at least 1700 evaluable patients (each observed for a minimum of 12 weeks), comprising of a minimum of 561 and 1005 patients treated with rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular AF (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of DVT and PE and prevention of recurrent thromboembolic events, respectively. In addition to the desire to study the use of rivaroxaban in a population that is more heterogeneous than those observed in clinical trials, it is desirable to put these observations into context. To characterise a population treated with existing anticoagulant therapy will allow the variation in determinants of treatment choices to be examined in relation to risk. Therefore, a similar number (at least 1700) of evaluable new user patients receiving alternative anticoagulant therapy will be recruited concurrently as an internal contextual cohort in order to characterise the adoption of rivaroxaban into clinical practice and explore possible differences in factors such as setting, prevalence of (non-clinical)[*] reasons for prescribing, physician prescribing preference factors[†] and those clinical characteristics which are known risk factors for the primary outcomes of interest.[6] This study will not inform on relative measure of risk of primary outcome between rivaroxaban and the internal contextual cohort. The key purpose of this internal contextual cohort is to explore the variation in the distribution and determinants of prognostic and clinical risk factors. The purpose is not to compare risk of primary outcome between the rivaroxaban and the internal contextual cohort; a much larger study is required for that.

Specialist HCP prescribers of anticoagulants from within the secondary care hospital setting will be systematically identified across the country, facilitated by existing clinical research

[*] Non-clinical reasons for prescribing include: factors associated with accumulation of authoritative evidence (formulary committee approval; recommendation from NICE; expert committee guidelines); patient request and/or prescriber expertise and history of clinical success with similar treatments .

[†] type of novel anticoagulant prescribed by the specialist HCP in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in clinical setting in previous calendar month.

networks, and will be invited to participate in the study prior to study start (exact date to be determined). These specialist HCPs will be informed that they will be participating in a cohort study which will monitor the use of a new entity oral antithrombotic agent (rivaroxaban) in accordance with requirements within the Risk Management Plan, [5] and existing therapy in patients with medical conditions that require anticoagulation. Data collection will be in two phases. After the clinical decision to start treatment with rivaroxaban or alternative anticoagulant therapy has been made by the HCP specialist, patients will be invited to participate in the study, be provided with patient study documentation and consent will be obtained. The specialist HCP will complete a summary of treatment details (including actual start date of anticoagulant treatment (hereafter denoted 'index date'), and demographic data as captured from existing medical charts. At least 12 weeks after index date a data collection end-of-observation questionnaire will be completed to collect information recorded in existing medical charts about early utilisation of rivaroxaban or alternative anticoagulant therapy and safety during the first 12 weeks of observation.

This study will enable the systematic collection and aggregated safety data reporting on patients newly initiated on treatment with rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting, with a particular focus on obtaining information on patients who stop taking rivaroxaban or switch to another anticoagulant prior to transfer of care to their GP. Its purpose will be to provide information on a large number of such patients and the treatment they received in the secondary care hospital setting.

The primary focus of the study will be to quantify the cumulative incidence (risk) of haemorrhage (within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed (Table 2)) and all intracranial sites) occurring in the 12 weeks observation period after treatment initiation for patients treated with rivaroxaban in real life clinical practice in the secondary care hospital setting. The secondary focus will be on 1) advancing the understanding of the patient population prescribed rivaroxaban in the secondary care hospital setting by exploring differences between rivaroxaban and the alternative anticoagulant therapy (contextual) cohort in the prevalence of non-clinical reasons for prescribing, prognostic and clinical risk factors for the selected risks of interest; 2) describing any prescribing and use of rivaroxaban outside terms of marketing authorisation ('off-label'), for example the approved indications and/or populations with special label precautions; 3) describing changes of health profile of patients, assessment of adherence, number of indication related episodes and duration, plus any alterations of the treatment programme for

either cohorts during the 12 week study observation period; 4) quantifying the risk of a) other major or minor bleeding outcomes not specified in the primary objectives b) all major and minor bleeds within a composite outcome, c) Haemorrhage (major bleeding during treatment (individual quantification per organ site) d) thromboembolism (recurrent and incident) and e) any other events‡ reported in the 12 week observation period overall and, if number of reports are sufficient, in patient subgroups of special interest in first 12 weeks of treatment under conditions of the routine secondary care hospital setting in the UK.

The study also includes (for rivaroxaban cohort only) several exploratory analyses to 1) where possible, to quantify the incidence of other important identified ,potential and special risks and outcomes of interest (such as severe abnormal liver function) not mentioned in the primary objective, other frequently and rarely reported adverse events during treatment with rivaroxaban and to identify previously unrecognized adverse drug reactions for rivaroxaban; and 2) describe clinical features and management of cases of overdose, major bleeding, VTE events indicating failure of anticoagulation and management of homeostasis in patients undergoing surgery (elective or urgent) during observation of the cohort exposed to rivaroxaban.

‡ The term 'event', as used in this study, is defined as, “any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any alteration of clinical importance in laboratory values, or any other complaint that was considered of sufficient importance to enter in the patient's medical charts.”

1.0 BACKGROUND

1.1 Post-marketing surveillance

The clinical safety information available when a new medicine is marketed relates to a limited number of patients.[7] This applies to new formulations of licensed medicines. Pre-marketing data will usually give little information on drug utilisation and safety post-marketing. There has been general agreement for more than 50 years of the importance of postmarketing adverse event monitoring and postmarketing safety studies in providing complementary information on the clinically necessary understanding of the safety profile of a drug. This has resulted in not only the establishment of voluntary systems for reporting suspected adverse drug reactions (ADRs), but the development of a range of other methods to monitor and study postmarketing drug safety. In the UK, the Yellow Card spontaneous reporting scheme and a prescription based monitoring process (Prescription-Event Monitoring (PEM) [8]) provide complementary systems of post-marketing surveillance on a national scale of newly marketed drugs prescribed by general practitioners (GPs) in the primary care setting. The theoretical basis for establishing a system to monitor events regardless of relatedness to drug exposure was proposed by Finney in 1965.[9] The principle of 'event monitoring' has since been adapted to monitor the use and safety profile of a new drug prescribed to a patient population under the care of specialist HCPs in the secondary care hospital setting (termed 'Specialist care Event Monitoring' (SCEM) studies).

1.2 Study rationale

The aim of this study is to actively monitor the short term (up to 12 weeks) safety profile and drug utilisation of rivaroxaban as prescribed to patients for medical conditions ('medical patients' - i.e. not those requiring VTE prophylaxis with elective surgery) requiring anticoagulation by specialist HCPs in the secondary care hospital setting in England and Wales. In the UK, often the choice of drugs prescribed in primary care is guided by clinical experience and recommendations from experts and therapeutic committees in secondary care hospital setting. The patient population who are under the care of specialist HCPs, include those who may be more complex in terms of underlying disease, co-morbidities and concomitant medications than in the general disease population. In particular, this methodology enables the capture of important information on patients who may discontinue treatment prior to transfer of care to general practitioners in the primary care setting and therefore, risk estimates will be less subject to the influence of selection bias based on

concurrent health status/disease severity by capturing first ever prescriptions from secondary care HCPs. Also, this method enables more reliable examination of exposures in relation to outcomes.

For this study, monitoring the target patient population will be achieved through an active research network of HCPs, established and maintained by the administration team at the DSRU and study research nurses/facilitators. Healthcare professionals responsible for prescribing anticoagulants (hereafter denoted 'specialist HCPs) in the secondary care hospital setting will be systematically identified directly by the DSRU and also through existing clinical research networks and will be invited to participate in the study prior to study start (February 2013 - exact date to be determined). Specialist HCPs will be informed that they will be participating in a cohort study which will monitor the extension of licence of a recently introduced oral antithrombotic agent (rivaroxaban), in accordance with requirements within the Risk Management Plan. [5]

Medical patients will be seen by specialist HCPs within the standard course of care (section 1.4) when initiating anticoagulant therapy. In the UK, the usual care pathway is such that it is anticipated that the initial follow-up of each individual patient will be handled by the specialist HCP. The patient may then continue to be managed by the specialist HCP and seen by them for their follow-up appointments on an 'out-patient' basis within the secondary care hospital setting, or they may be discharged and ongoing care transferred to their primary care physician (GP). This depends on factors specific to each individual case. Once the pharmacotherapeutic treatment decision has been made, and either rivaroxaban or alternative anticoagulant therapy prescribed as the most appropriate treatment, the patient will be invited to participate in the study. Consent will be required for access to information from existing secondary care hospital charts, and also to enable contact with their GP to access information from existing general practice primary care charts. The patient observation period will be for the first 12 weeks after starting anticoagulant treatment ('index date') to capture initial use in all target subsets of interest, and similarly for new user anticoagulant therapy patients.

1.3 Rivaroxaban formulation and licensed prescribing indications

Rivaroxaban, a highly selective direct factor Xa inhibitor, was approved by the European Commission on 30 September 2008 for the prevention of venous thromboembolism (VTE) in

adult patients undergoing elective hip or knee replacements. [1] On 19 December 2011, the European Commission approved the use of Xarelto for the indication prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) (with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack), and for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.[2] A further variation of marketing authorisation for the treatment of PE, under the label 'Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults' was approved on 20 November 2012 [3] More recently, a marketing application has been approved in the EU for rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.[4]

Rivaroxaban is a highly selective direct factor Xa inhibitor with high oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated. It is formulated as a film-coated tablet containing 10 milligram (mg), 15mg or 20mg of active ingredient for oral administration. The absolute bioavailability of rivaroxaban is high (80 % - 100 %) for the 10 mg dose, with peak plasma levels attained between 2-4 hours.[1]

1.3.1 Dosage and duration

Duration depends on individual risk of patient for VTE and stroke, which is determined by indication for treatment (Table 1).

Table 1. Dosage and duration of treatment with rivaroxaban according to licensed and proposed indications. [1;5;10-12]

Indication	Initial dose (mg)	Maintenance / maximum dose	Duration	Food intake
Prevention of VTE in adult patients undergoing elective major hip or knee replacement surgery	10 Initial dose should be taken 6 to 10 hours after surgery provided that haemostasis has been established	10	For patients undergoing major hip surgery, -5 weeks For patients undergoing major knee surgery - 2 weeks	Can be taken with or without food
Treatment of DVT and prevention of recurrent DVT and PE in adults	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of PE and prevention of recurrent DVT and PE in adults	15 (twice daily for first 3 weeks)	20 (daily)	Continued treatment	To be taken with food
Treatment of DVT and prevention of recurrent DVT and PE in adults (in patients with moderate or severe renal impairment) [§]	15 (twice daily for first 3 weeks)	15 (daily)	Continued treatment	To be taken with food
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	20 (daily)	20 (daily)	Continued treatment	To be taken with food
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 (in patients with moderate or severe renal impairment)	15 (daily)	15 (daily)	Continued treatment	To be taken with food

[§] In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:
For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling

1.3.2 Safety Profile and Undesirable Effects

The clinical trial safety profile data for rivaroxaban for prevention of VTE in patients undergoing elective hip or knee replacement is based on the RECORD trials [13] [14-16] For the new indications of treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) in adults, treatment of PE and prevention of recurrent DVT and PE in adults and prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, additional clinical trials have been performed. [10;17-20] The role of rivaroxaban for the treatment of VTE was investigated in three large randomised trials in the EINSTEIN programme: the EINSTEIN-DVT study was planned to probe the role of rivaroxaban as a standalone drug for the treatment of acute DVT; the EINSTEIN-Extension study was designed to evaluate extended anticoagulation treatment with rivaroxaban in patients who have been treated for acute VTE; and the EINSTEIN-PE study evaluated the role of rivaroxaban for the treatment of acute PE. The ROCKET-AF trial was designed as double-blind, double dummy trial comparing rivaroxaban with warfarin for the prevention of stroke and thromboembolic events in people with non-valvular atrial fibrillation at risk of future thromboembolic events. Approximately 80,000 individuals (receiving rivaroxaban, comparator and placebo) have been recruited to rivaroxaban clinical studies to date. [5]Additional information from larger numbers outside the clinical trial setting, in conditions of routine clinical practice, may be helpful to further monitor possible adverse events in users of rivaroxaban. A Risk Management Plan has been developed for rivaroxaban by the MAH. This plan includes tools designed to monitor the important risks (including class effects and off-label use). The current safety specification (important risk, potential risk, missing information) is based on the Xarelto EU RMP version 7.5. [5]

Important identified risks, including class effects, are

- Haemorrhage

Important potential risks, including class effects, are

- Embryo-foetal toxicity

Important missing information includes:

- Patients undergoing major orthopaedic surgery **OTHER** than the approved indication "elective hip or knee replacement surgery[**]"
- Patients with severe renal impairment (CrCl <30ml/min)
- Patients receiving concomitant systemic treatment with CYP3A4 or P-gp inhibitors 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 AF and a prosthetic heart valve
- long term therapy with rivaroxaban in treatment of DVT, PE and SPAF in real-life setting.
- Patients < 18 years

Outcomes of special interest

- Increase in liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], Gamma-Glutamyl Transferase (GGT)] and bilirubin
- Management of homeostasis in patients with the indications of interest who also undergo surgery (elective or urgent) during the observation period in this study.

The safety profile and efficacy of rivaroxaban in children aged <18 years have not been established. No data are available. Therefore, rivaroxaban is not recommended for use in children below 18 years of age. [1] A Paediatric Investigation Plan (PIP) has been agreed with EMA, the aim of which is to contribute to the insight in the efficacy and safety profile of rivaroxaban in paediatric populations.

Off label prescribing of rivaroxaban (in terms of medical indication, dose etc) is possible so any data relating to off label use will be examined in this study.

1.4 Anticoagulant Therapy

In the UK, evidence based guidelines provide recommendations to practitioners to support pharmacotherapeutic decision making. These are summarised in the sections below.

[**] This study is not designed to monitor the safety and use of rivaroxaban in this group of off-label **surgical** patients. However since there is a need to inform on off-label use in non-orthopaedic medical conditions requiring anticoagulation, data from any patients within this latter category will be eligible for inclusion and evaluated as part of the secondary objective (ii) in Section 2.2.2

1.4.1 Atrial Fibrillation

For the diagnosis and management of patients with AF who are either post-stroke, or have had a TIA the following standard pharmacotherapeutic treatments are recommended:

- warfarin should be administered as the most effective thromboprophylactic agent
- aspirin or dipyridamole should not be administered as thromboprophylactic agents unless indicated for the treatment of comorbidities or vascular disease. [21]

1.4.2 DVT/PE

A choice of low molecular weight heparin (LMWH) or fondaparinux should be offered to patients with confirmed proximal DVT or PE, taking into account comorbidities, contraindications and drug costs with the following exceptions:

- For patients with severe renal impairment or established renal failure (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2) offer unfractionated heparin (UFH) with dose adjustments based on the APTT (activated partial thromboplastin time) or LMWH with dose adjustments based on an anti-Xa assay.
- For patients with an increased risk of bleeding consider UFH.
- For patients with PE and haemodynamic instability, offer UFH and consider thrombolytic therapy.

The LMWH, fondaparinux or UFH should be started as soon as possible and continued for at least 5 days or until the international normalised ratio (INR) (adjusted by a vitamin K antagonist [VKA]) is 2 or above for at least 24 hours, whichever is longer.[22]

The Scottish Intercollegiate Guidelines recommend that after the first episode of limb deep vein thrombosis, continuation of anticoagulation with an oral anticoagulant (warfarin) is required as maintenance treatment. The aim is to minimise the risks of PE, recurrent DVT and post thrombotic syndrome (PTS) [23]

The British guideline on oral anticoagulation with warfarin recommends that:

- first episodes of VTE should be treated with an INR target of 2.5 - the target range should not be lowered for patients who require anticoagulation beyond 3 months
- recurrent VTE whilst anticoagulated and within the therapeutic range should be managed by increasing the INR target to 3.5

- patients with proximal DVT or PE should be treated for at least 3 months to prevent extension of thrombus and recurrence. [24]

1.5 Considerations in initiating anticoagulation treatment, stroke and bleeding risk

For this study, it is important to capture information on a patient's stroke and bleeding risk score as derived from information within existing medical records relating to index date and end of observation, so that any changes in risk of either can be examined in relation to changes in factors associated with clinical condition.

The $CHADS_2$ classification scheme is a clinical prediction rule (an acronym for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or transient ischemic attack) that estimates the risk of stroke in patients with non-rheumatic atrial fibrillation.[25;26] Its use is advocated by the National Institute for Health and Clinical Excellence (NICE) to determine whether or not antithrombotic therapy should be initiated based on patient-specific stroke risk.[27] The classification scheme assigns a score (0 to 6; one point each for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus and two points for prior Stroke or transient ischemic attack) based on the number of risk factors an individual patient has; a high $CHADS_2$ score corresponds to a greater risk of stroke such that a score of 2 and above indicated the need for oral anticoagulation therapy, while a low $CHADS_2$ score corresponds to a lower risk of stroke, whereby other risk modifiers should be considered.

To complement the $CHADS_2$ score, by the inclusion of additional 'stroke risk modifier' risk factors, the CHA_2DS_2-VASc score has been proposed. [25;26;28] These additional non-major stroke risk factors include age 65-74, female gender and vascular disease. In the CHA_2DS_2-VASc score, 'age 75 and above' also has extra weight, with 2 points.

In clinical practice, bleeding risk assessment should be performed prior to initiation of oral anticoagulation therapy. A validated bleeding risk score which is included within the European Society of Cardiology (ESC) Guideline for management of AF patients is the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) bleeding risk schema, whereby a score of ≥3 indicates "high risk" and some caution and

regular review of the patient is needed. Note that knowledge of INR control is needed to assess the 'labile INR' criterion; otherwise for a non-warfarin patient, this scores zero.

In the UK, a NICE clinical guideline is available which outlines assessment of risks of VTE and bleeding in medical patients admitted to hospital. [29] It advocates a form of benefit risk assessment of offering VTE prophylaxis to medical, surgical and /or patients with trauma balanced against risk of VTE and bleeding. It also states that choice of pharmacological VTE prophylaxis should be based on local policy, clinical condition and patient preference. Thus it is important to examine whether the likely hierarchical clustering of patients –by region geographically and by medical institution has any impact on either bleeding risk assessment or incidence of haemorrhage.

2.0 AIMS AND OBJECTIVES OF STUDY

2.1 Overall aim:

To monitor the short-term (12 weeks) use and safety profile of rivaroxaban prescribed to new-user adult patients (i.e. rivaroxaban naïve who may or may not be antithrombotic therapy naïve) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, the treatment of DVT, PE, and the prevention of recurrent DVT and PE in adult patients, requiring anticoagulation under normal conditions of use in the secondary care hospital setting. In addition since it is desirable to put these observations into context and characterise a population treated with existing anticoagulant treatment to allow the variation in determinants of treatment choices to be examined in relation to risk, a similar number of evaluable patients receiving alternative anticoagulant therapy will be monitored in order to inform on the adoption of rivaroxaban into clinical practice.

2.2 Specific objectives:

2.2.1 The primary objective

Its purpose is to provide timely information on:

(i) Estimation of the cumulative incident risk (separately) of the following important identified risk for rivaroxaban users which is:

- Haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (Table 2))

2.2.2 Secondary Objectives

These are given below. Their purpose is to provide timely information on:

(i) Prescriber and cohort accrual and the type of prescriber responsible for, and the setting of initiation of treatment with either rivaroxaban or alternative anticoagulant therapy.

(ii) Prevalence of non-clinical reasons for prescribing, prognostic health factors and clinical risk factors for haemorrhage as reported in medical charts for patients undergoing anticoagulation with either rivaroxaban or alternative anticoagulant therapy in the secondary care hospital setting and the treatment programme they received to advance the understanding of the patient population prescribed rivaroxaban in actual clinical practice in the secondary care hospital setting

(iii) Changes of health profile of patients, assessment of adherence, plus any alterations of the treatment programme during the 12 week observation period, as recorded in medical charts.

(iv) To quantify the risk of:

(a) (separately) haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites for contextual anticoagulant therapy cohort

(b) all major bleeding specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort (as composite)

(c) (separately) haemorrhage (major bleeding according to Table 2) within critical organ sites other than specified in primary objective for both rivaroxaban and contextual anticoagulant therapy cohort

(d) all major and clinically relevant non-major bleeds (as a composite outcome)

(e) thromboembolic complications (incident and recurrent)

(f) other[††] events including special outcomes of interest (severe hepatic failure and abnormal LFTs above 3x ULN) as recorded in medical charts during the 12 week observation period and, if number of reports are sufficient, in patient subgroups of special interest, including:

- reported indications
- elderly (>= 65 years)[‡‡], other contraindicated or special groups (e.g. pregnant and breastfeeding women, patients with concurrent significant renal or hepatic impairment; patients with known VTE and/or haemorrhagic risk factors e.g. congenital or acquired bleeding disorders, uncontrolled severe arterial

[††] Other than major and clinically relevant non major bleeding outcomes, or thromboembolic complications (recurrent or incident)

[‡‡] Children and adolescents aged less than 18 years of age will be excluded from the SCEM study. Since this is important missing information, data on this special population will be captured within the complementary M-PEM, if reported.

hypertension, active ulcerative gastrointestinal disease) and off-label groups (patients with other non-orthopaedic medical conditions)

- concomitant use of medications that are contraindicated or to be used with caution (e.g. CYP3A4 inducers/inhibitors, P-gp inhibitors, anticoagulants, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, hormone and oral contraception therapy and platelet aggregation inhibitors)

2.2.3 Exploratory objectives (for rivaroxaban only)

The specific objectives that follow are all exploratory. The purposes of these objectives are:

(i) Where possible, to quantify the incidence of other important identified and potential risks (not mentioned in objective 2.2.1), other frequently and rarely reported adverse events as recorded in the medical charts and to identify previously unrecognised ADRs

(ii) To describe clinical features and management of cases of overdose, major bleeding (according to pre-specified definition (Table 2), VTE events indicating failure of anticoagulation and management of homeostasis during surgery as recorded reporting the medical charts in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.

Table 2. Haemorrhage outcomes[30]

A major[†] bleeding event will be defined using ISTH criteria (21) as clinically overt bleeding that is associated with:
• A fall in haemoglobin of 2 g/dL or more, or • A transfusion of 2 or more units of packed red blood cells or whole blood, or • A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or • A fatal outcome
A clinically-relevant non-major bleeding event is defined as an overt bleeding event not meeting the criteria for a major bleeding event, but associated with medical intervention[§§], unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life.
Examples of non-major clinically relevant bleeding events are:
• Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding, i.e., no spots on a handkerchief, within 24 hours), or leads to an intervention (packing, electrocautery, etc.) • Gingival bleeding if it occurs spontaneously (i.e. unrelated to tooth brushing or eating), or if it lasts for more than 5 minutes • Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract • Macroscopic gastrointestinal haemorrhage: at least 1 episode of melena or haematemesis, if clinically apparent • Rectal blood loss, if more than a few spots • Haemoptysis, if more than a few speckles in the sputum, or • Intramuscular hematoma • Subcutaneous hematoma if the size is larger than 25 cm 2 or larger than 100 cm^2 if provoked • Multiple source bleeding events

[†] *The three organ sites included in the primary objective are gastrointestinal and, urogenital (which meet the criteria for major bleed) and intracranial. Case definition will be confirmed by project steering committee prior to patient recruitment.*

[§§] Such as: Surgical or endoscopic intervention; decompression of a closed space to stop or control the event; protamine sulphate administration

3.0 ETHICAL CONSIDERATIONS

All studies carried out by at the DSRU will be conducted in accordance with national and international guidelines. [31;32] For this cohort study, ethics approval via IRAS (integrated research application system) in the UK will be required. Participating specialist HCPs will be asked to provide patients with documentation (with a unique study reference code). Patient study documentation will include an patient information sheet about the study which will describe that their secondary care medical charts will be accessed during the time-frame of active study data collection by the specialist HCP and/or DSRU research staff in order to extract exposure and outcome data relevant to the 12 week observation period, *** and also that their primary care medical charts may be accessed (*contact details to be provided on the consent form*), if they are discharged to the care of their GP within the 12 week observation period. It will also provide contact details of the DSRU study team if they have any questions.

Specialist HCPs will provide patients with a consent form so that patients can consider and give consent for their participation within this project. The consent form will stress confidentiality, that no specific details of their treatment will be released to external parties, that the patient may withdraw consent at any time by contacting either the specialist HCP or the DSRU study research team directly, and that the patient will not be asked to attend clinics more than usual or undergo any additional treatment or questioning. The consent form will also request information to be provided on patient ethnicity, current marital status, current employment status, smoking and alcohol use. This is optional and will be used to inform on representativeness of study cohort. Three signed copies are required. Those patients who wish to inform the DSRU immediately of their decision will give the signed consent form to the specialist HCP. They in turn will send the original to the DSRU, retain one copy for their records and issue a copy to the patient. Where a patient is unable to sign the consent form (e.g. because of weakness of the dominant hand following stroke), consent will be confirmed orally in the presence of a witness (an individual other than the person taking consent) who will sign the consent form on behalf of the participant.

For those patients who wish to have a further opportunity to reflect on their participation, the specialist HCP will ask the patient to complete a 'consent to contact' form, which will enable DSRU study research staff to contact the patient through their preferred route of contact (surface post, email, or telephone) after a period of at least two days to obtain consent. This

*** The exception will be if a female patient becomes pregnant, the outcome of the birth will be requested.

will be the only point at which DSRU research staff will contact the eligible patients directly. If the patient agrees to participate, they will sign the consent form , retain a copy and send the original and one further copy via surface mail to the DSRU study coordinating centre, or, if preferred, to the specialist HCP (who will then submit the original form to the DSRU). Receipt of the signed consent to contact form or the fully completed consent form (if patient provides immediate consent) by the DSRU study team should be within 4 weeks after index date, if possible.

In addition, within the same time frame, the specialist HCP will be asked to summarise selected data from the medical charts (non-clinical reasons for prescribing, demographic and treatment details) using a simple questionnaire (anonymised using the patient's allocated study reference number) and send these data to the DSRU coordinating centre either through a secure electronic website, or via surface mail.

3.1 Consent for patients without mental capacity

We wish to include patients who do not have mental capacity and who are therefore unable to consent for themselves. This would include patients who have had a stroke, have cognitive impairment, dementia and/or learning difficulties. Due to the nature of the indication for use, many patients with these conditions may be prescribed rivaroxaban and these are patients who may be unable to consent for themselves but are still at risk of adverse events and therefore should be included. Exclusion of patients with mental incapacity would mean exclusion of a group of potentially high risk patients.

For potential patients who lack mental capacity to consent to research, a medically qualified member of the care team will identify a personal consultee to approach and discuss the study with. This will be a person who is in a position to advise on the wishes and feelings of the potential patient in relation to taking part in this research project. It is anticipated that the personal consultee would be a family member or friend. In the situation where no family member or friend is willing and able to act as a consultee, a nominated consultee will be sought following the local arrangements in situ. This will be a person who has no connection with the project and who is willing to be consulted about the participation of the person who lacks capacity in the research project. In the situation where consent is being sought out of hours and there is no nominated consultee available, the process can wait until a suitable person is available.

The identified consultee will be provided with a consultee information sheet (there will not be a separate information sheet for the nominated consultee, if they wish to view a copy then they can request a copy of the personal consultee information sheet) and will also have an opportunity to ask

questions. The consultee will then be asked to complete a consultee declaration form if they believe the patient would have no objection to taking part in the study.

If a patient regains capacity during their participation in the study, they will be informed about the study, given a patient information sheet and asked to provide their own consent in the normal way. If a patient does not wish to continue in the study, they will be withdrawn.

4.0 METHODS

4.1 Study Design & Time frame

This study will be a registry-based observational, population-based cohort study with an internal contextual cohort utilising the technique of cohort event monitoring to study the short-term (up to 12 weeks) safety profile and use of rivaroxaban prescribed by specialist HCPs in the secondary care hospital setting in the immediate post-marketing period for the licence extension. Twelve weeks observation is regarded as a period of time sufficient for data from all relevant patient populations (which informs on any post start of observation health events related to short-term exposure that they might have experienced) to be recorded in the patient's medical charts by specialist HCP. Randomisation will not be required. Once the pharmacotherapeutic treatment decision has been made, and either rivaroxaban or the alternative anticoagulation therapy prescribed as the most appropriate treatment based on clinical need, a patient will be invited to participate in the study and consent obtained for access to information from medical charts (see section 3.0).

Study start is defined as the date that the first patient is recruited into the study, which is anticipated to begin May 2013 (*exact date to be confirmed*) and continue for a maximum of 36 months, or until the target sample size for both cohorts has been achieved (whichever is the soonest); see section 4.2. The final cohort sizes, period of observation and the duration of the SCEM study will be dependent on the level of prescribing of rivaroxaban by specialist HCPs in England and Wales (see section 4.2). Data collected during later time periods can be compared with earlier periods to identify any trends that may be emerging. Slow uptake may impact on the ability to meet the study objectives; in this instance the need to continue data collection, extend the observation period and the feasibility of study completion within the proposed time frame should be open to re-evaluation.

Period of observation for analyses will commence from index date (i.e. actual start date of anticoagulant treatment, not the date first seen by the specialist) and continue for 12 weeks (or less if patient discontinues to be under the care of the specialist HCP; to be established via the 12 week end of observation questionnaire) in order to allow for detection of outcomes associated with oral anticoagulant treatment initiation as recorded in medical charts. This study will also collect information on exposure to any other medicines (including those given as part of acute care management within the four calendar weeks prior to index date) as recorded in medical charts in order to explore impact of those treatments on outcomes of interest. Since patient care is likely to be shared between secondary and primary care for most patients during the 12 week observation period, the patient's GP will be contacted[†††] to complete a simple questionnaire to collect any information on outcomes of interest that have been recorded in the patient's medical charts held in primary care during the 12 week observation period to minimise under-reporting on selected outcomes. Where additional outcomes are identified that have not be reported by the initiating prescriber, these will be followed-up with the GP to ascertain further information.

4.2 Sample size

4.2.1 Sample size for primary outcome (haemorrhage – within intracranial, gastrointestinal and urogenital critical organ sites) where expected cumulative incidence is known

Where studies, such as clinical trials, have already estimated the impact of the exposure on the outcome of interest, the one objective of this observational study is to be able to estimate the measure of frequency so that it lies within a range (margin of error) close to the estimate from the RCT, assuming this represents the true value. Ideally this margin of error (also called precision) should be as narrow as possible, so that the frequency is estimated as precisely as possible [33], for example the margin of error is equal to half the width of the confidence interval. for the frequency estimate As such, in this study it is more appropriate to choose a sample size that will yield a confidence interval of a predefined width for those identified risks defined within the primary outcome which are of greatest clinical and medical importance i.e. major bleeding outcomes (Section 2.2.1). Table 3 displays the samples sizes (95% confidence intervals) across a range of expected incidences and levels of precision.

[†††] Overlap of data collection between SCEM and M-PEM should minimise any under-reporting of events of interest associated with the primary objective. However due consideration should be given to a) possible non-response of GPs for the long-term M-PEM study that might arise from the GP's knowledge that the patient is participating in the SCEM and b) that some patients are managed by specialist GPs purely on an outpatient basis and thus may never be officially admitted to hospital . The emphasis must be made that the two studies are complementary and participation in both is highly desirable.

From rivaroxaban clinical trial data, the cumulative incidence of each of the primary outcome major bleeding events (GI, urogenital and intracranial) in patients taking rivaroxaban for DVT and prevention of recurrent DVT and PE over 12 weeks of treatment was approximately 0.2%, 0.1% and 0.0%, respectively. Since information on the reported incidence for intracranial major bleeding outcomes within the first 12 weeks of treatment is limited, the reported incidence of intracranial haemorrhage with enoxaparin/vitamin K antagonist (VKA) from RCTs of 0.1% within 12 weeks will be used as an estimate of the incidence of that event in this population for rivaroxaban. From clinical trial data, the cumulative incidence of the primary outcome major bleeding events was similar in patients taking rivaroxaban for PE (~0.3%). As such, we do not expect any difference in cumulative incidence of bleeding between PE and DVT patients.

The formula used to calculate the sample size based on an estimation of the proportion of patients who will experience major bleeding outcomes is[33]:

$$\text{Sample size} = \frac{3.84 \times p(1-p)}{(\text{precision})^2}$$ where p= estimated proportion (cumulative incidence)

Thus in this population of patients taking rivaroxaban for the treatment of DVT and PE and prevention of recurrent DVT and PE, in order to estimate the expected (true) cumulative incidence of the primary outcomes of major bleeding (GI, urogenital and intracranial) of 0.4% (0.2%, 0.1% and 0.1%, respectively), within +/- 0.39%, we would need a sample size of 1005 patients (Epi Info v6).

The cumulative incidence of each of the primary outcome major bleeding events (GI, urogenital and intracranial) in patients taking rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation over 12 weeks of treatment was approximately 0.5%, 0.1% and 0.1%,‡‡‡ respectively. [5] Thus, in this population of patients taking rivaroxaban for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, in order to estimate the expected (true) cumulative incidence of the primary outcomes of major bleeding (GI, urogenital and

‡‡‡ Approximate estimates of cumulative incidence in 12 weeks of treatment, based on steady increase in incidence over time and overall cumulative incidence from a median of 590 days treatment exposure (90/590*N)

intracranial) of 0.7% (0.5%, 0.1% and 0.1%, respectively), within +/- 0.69%, we would need a sample size of 561 patients.

Thus, in summary, for this study, a minimum sample size of 1700 evaluable patients for rivaroxaban is desirable to ensure the minimum of 1005 and 561 patients is achieved for each of the two indications described above for each drug, based on ratio of 1:2 respectively, with 12 weeks observation period sufficient to estimate cumulative incidence of specified primary outcomes of interest with desired precision. A similar number of evaluable new user alternative anticoagulant therapy patients will be collected for the internal contextual cohort.

In this study, sample size has been calculated such that the study estimate of cumulative incidence of major bleeding within each indication should fall with a pre-specified proportion which is relative to the true value. There is no ideal precision which should be used when calculating sample size, so use of proportion as an indicator of relative precision ensures the margin of error remains appropriate to the estimated size of cumulative incidence of major bleeding events.

Table 3. Sample sizes of evaluable patients required to estimate the expected (true) cumulative incidence of a specified adverse event with 95% confidence intervals of different precisions (0.2% to 5%).

Incidence from RCT (%)	Precision 0.20%	Precision 0.39%	Precision 0.50%	Precision 0.69%	Precision 1%	Precision 2%	Precision 3%	Precision 5%
0.10	958	252	153	81	38	10	4	2
0.20	1913	504	307	161	77	19	9	3
0.30	2864	755	459	241	115	29	13	5
0.40	3812	1005	612	321	153	38	17	6
0.50	4755	1255	764	401	191	48	21	8
0.70	6631	1752	1067	561	267	67	30	11
0.80	7564	2000	1218	640	305	76	34	12
1.00	9418	2494	1519	798	380	95	42	15
2.00	18475	4926	3003	1579	752	188	84	30
3.00	27187	7296	4452	2342	1117	279	124	45
4.00	35566	9605	5866	3089	1473	369	164	59
5.00	43627	11854	7246	3818	1821	456	203	73

4.2.2 Sample size for general safety surveillance of other events (aside from the primary outcome) where background rate is unknown.

For purposes of general safety surveillance (for events arising from exploratory objective (Section 2.2.3 (iii)) for the population of interest (i.e. those prescribed rivaroxaban according to labelled new indications), it is possible to estimate a sample size necessary to detect a minimum of three cases[§§§] based on an assumed rate in that exposed sub-group and assuming the background rate is zero. [35] For this study, a sample size of at least 1700 evaluable patients (see section 4.3.2.3) should allow for the detection of at least three cases of an event if it occurs with a rate of at least one in 200, with 99% probability. [35]

4.3 Study Population

4.3.1 Phase 1: Selection of specialist HCP

Since it is known that managed entry of rivaroxaban into the NHS exists (to assist organisations in developing medicines management policies and to inform prescribing decisions) the accessible secondary care settings will be those for which recommendations for prescribing rivaroxaban have been adopted. Thus the actual secondary care hospital settings will be a subset of all secondary care hospital settings in England and Wales. A representative sample [****]of specialist healthcare professionals responsible for prescribing anticoagulants ('specialist HCP') for medical conditions that require anticoagulation within those accessible settings will be systematically identified by the DSRU and will be invited to participate in the study prior to study start (anticipated May 2013, to be determined). This non-probability sampling method will be used because a probability sampling framework is not feasible as stated above.

Routes of identifying relevant specialist HCPs within these accessible settings will include the use of the existing clinical research networks and support networks provided by allied healthcare professionals, including hospital pharmacists, some of whom are highly specialised anticoagulation pharmacists working in secondary care hospital settings across England and Wales.

– [§§§] In many situations involving rare reactions it is assumed that the frequency of the event is small, so that the occurrence of the event follows a Poisson distribution and the 95% confidence interval (CI) calculated based on the number of events. If no events are observed in a study of X individuals then one can be 95% certain that the event occurs no more often that 3/X. [34]

[****] Representativeness of specialist HCPs will be considered in terms of geography, secondary care setting (teaching, general, private, outpatient only).

Specialist HCPs will be informed that they will be participating in a cohort study which will monitor the extension of licence of a recently introduced oral antithrombotic agent (rivaroxaban), in accordance with requirements within the Risk Management Plan for that product. Using a bespoke website, specialist HCPs will be required to register online with the study co-ordinating centre (DSRU) in order to receive access to relevant study documentation. Each participating specialist HCP will be requested to make treatment decisions independent of the study and then to evaluate whether a patient is eligible for inclusion based on broad entry criteria (see below).

Remuneration, in line with the standard British Medical Association (BMA) rate will be paid to the NHS trust to cover time and administration costs incurred (either by specialist HCPs or associated staff) to assist with obtaining consent and completing questionnaires.

4.3.2 Phase 2: Selection of patients

The accessible study population will be that portion of the target population of interest to whom participating specialist HCPs have access. The identification of the actual study population, (which will be a subset of the accessible study population) will be through (non-probability) systematic sampling whereby all consecutively identified†††† eligible new user patients treated by any specialist HCP (after the pharmacotherapeutic treatment decision has been made that one of the two study oral anticoagulants is the most appropriate treatment based on clinical need) and who provide consent (see section 3.0) will be enrolled until the desired sample size is reached. This method will be used because a probability sampling framework is not feasible and because participation within the study is not required as a condition of receiving treatment. This approach is intended to reduce conscious or unconscious selection bias on the part of the specialist HCP as to whom to invite to participate in the study, especially with regard to prognostic factors that may be related to prognosis.

New users of rivaroxaban will be comprised of rivaroxaban naïve patients, who may or may not be antithrombotic or anticoagulant treatment naive patients newly initiated by specialist HCPs. The patient may then have medicines management transferred to the GP in primary care. Thus, the GP may take on the primary role of monitoring treatment, providing prescriptions and altering the dose when necessary, with the option of referral to secondary

†††† As relevant to the date that the specialist HCP registers to participate in the study

care if and when required. Alternatively, the patient may be primarily managed within the secondary care setting alone.

The contextual cohort will be comprised of patients for whom no exposure to anticoagulation therapy has occurred within the 12 months prior to initiation by the Specialist HCP for the current study. Clinical care pathway will be the same as that outlined above for rivaroxaban patients.

Since this is a new user inception or incidence rivaroxaban cohort that is being identified, this study avoids the introduction of a number of biases associated with existing users (including incidence/prevalence bias, survivorship bias, and follow-up bias) which may impact on the measure of frequency of primary objective. Data will also be available for the internal contextual cohort which will have been collected during the same calendar period, for similar indications using the same data collection methods, and all subject to the same protocol. This minimises effect of bias from non-random measurement error. However, whilst users of anticoagulant therapy appear to provide a 'logical' contextual cohort that may be similar with regard to some clinical risk factors, they may also differ with respect to other important confounding factors such as disease severity. The key purpose of this contextual cohort is to explore the variation in the distribution and determinants of prognostic and clinical risk factors. It is not to compare risk of primary outcome between the two groups.
The first part of the second phase of the study will involve participating specialist HCPs capturing (in anonymised format using patient unique identifier) brief summary data (e.g. sex, age, indication, bleeding/stroke risk score and non-clinical reasons for prescribing) as recorded in the medical charts for **all** individuals invited to participate (including those who declined) for whom the clinical decision to prescribe rivaroxaban or alternative anticoagulant therapy was made under conditions of real life practice. These data will help examine the representativeness of the study population.

Cohort recruitment will be examined regularly to monitor the number of evaluable patients included, so as to ensure that the desired ratio of 1:1 rivaroxaban: contextual cohort patients with the relevant indications is achieved in the final overall study cohort for secondary objective analysis.

4.3.2.1 Patient Inclusion Criteria

Since this is an observational cohort study conducted in a naturalistic setting, open patient entry criteria apply to maximise external validity. General inclusion criteria are: ‡‡‡‡

- age 18 years or above after study start§§§§
- index date on or after study start
- signed, informed consent
- patients treated for DVT or PE
- patients with non-valvular AF (with one or more risk factors) treated for prevention of stroke and systemic embolism

4.3.2.2 Patient Exclusion Criteria

Specific exclusion criterion for the alternative anticoagulant therapy cohort is:

- Any use of univalent direct thrombin inhibitor or direct factor Xa inhibitors.
- use of anticoagulant therapy or other vitamin K antagonists recorded within one year prior to index date.*****

4.3.2.3 Evaluable patients.

Evaluable patients are those patients who have provided consent and for whom analysable clinical data has been provided in the data collection questionnaires. Evaluable patients for whom the second phase (12 week) survey questionnaire (from BOTH specialist HCP and GP) is returned blank (contain no clinical information) or has not been returned will only be included for analysis of secondary objectives (i) and, (ii).

Consented patients will not be considered evaluable if the specialist HCP reports that the patient did not take rivaroxaban or alternative anticoagulant therapy. If there is evidence to suggest duplication of patients, either through inadvertent duplication between different specialist HCPs within the same clinical setting, or if a patient was switched from rivaroxaban to alternative anticoagulant therapy, or there is a significant delay (>1 month) in receipt of phase 1 survey form then the patients identified will be considered for inclusion on a case by case basis by the study manager and/or project advisory committee.

‡‡‡‡ Any cases in which there is ambiguity relating to the indication for treatment will be reviewed on a case by case basis, in order to confirm the prescribing indication/indications.

§§§§ However, a patient under the age of 18 will be included in the study if, in what is expected to be rare situations, a doctor decides on the basis of his/her clinical judgement to prescribe rivaroxaban for such person.

***** patients will be excluded if they are being treated with antiplatelet therapy exclusively

Patients will be automatically withdrawn if the patient or specialist HCP provides informed written or verbal notification that they no longer wish to participate at any stage of the study.

4.4 Data Collection

Medical charts-based data collection in this study will be conducted in various phases; relevant documentation (such as information leaflets, questionnaire, consent forms, etc) will be available both as hard copies and electronically for download by the participating specialist HCP.

4.4.1 Data Collection Methods

4.4.1.1 Recruitment

The first phase will have two parts.

Part 1: Recruitment of eligible specialist HCP.

Demographic and prescribing preference data on specialist HCPs (see below) will be collected upon registration with the DSRU. The DSRU will allocate a unique HCP study reference number to each participating specialist HCP for study audit and data management processes.

Part 2: Recruitment of eligible patients initiated with the study drug under clinical care of participating specialist HCP.

For all eligible patients invited to participate, the specialist HCP will be asked to create a patient log to record anonymously (using the study patient reference number provided on patient study documentation issued), demography (age and sex), indication, treatment given and presence of known pre-existing risk factors for stroke and bleeding as derived from data within existing medical charts. This log will be submitted to the DSRU coordinating centre either through a secure online website, or via surface mail. . The unique study reference number allocated to each patient will be used for study audit and data management processes.

4.4.1.2 Exposure/outcome data collection

The second phase will also have two parts.

Part 1: At least twelve weeks post index date, the specialist HCP will be prompted to complete a questionnaire which will gather information recorded within medical charts on medical history and medication use prior to or present on index date; changes on general health and medications during treatment, clinical events of medical interest and serious

adverse event reports [classified using the International Conference on Harmonisation definitions [36]]. For patients for whom the specialist HCP reports that the patient was discharged to primary care for continued treatment during the 12 week observation period, the patient's GP will be contacted to complete an abridged end of survey 12 week questionnaire using data recorded within primary care medical charts.

Part 2. Events of interest will undergo aggregate assessment of drug-relatedness, which may include follow-up using event-specific questionnaires sent to the specialist HCP (see 4.4.2.3) or GP. These events will be assessed for drug-relatedness by DSRU staff.[37] With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection for this study from medical charts will occur post the survey period.

4.4.2 Data Collection

4.4.2.1 Specialist HCP

The following data will be collected for specialist HCPs upon recruitment into the study

1. Demographic characteristics; (age, sex, ethnicity, year of first registration as HCP and awarding institution, year of first registration as specialist and awarding institution, year of start of employment at current institution)
2. Setting- (e.g. inpatient hospital ward, outpatient clinic);
3. Institution type (teaching, general, private) and region of location
4. Specialist HCP preference factors (type of novel anticoagulants prescribed in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in previous calendar month)
5. Participation response/non-response rates (of eligible specialist HCPs within relevant existing research networks where available).

4.4.2.2 Eligible patient index date information

For all eligible patients invited to participate, the following anonymised information will be collected using information contained within medical charts.

- demographic characteristics (age, gender)
- Reasons for prescribing (clinical judgement, recommendation from NICE, expert committee guidelines, trust formulary committee guidelines, Patient Group Direction in anticoagulation clinic, potential ease of reversibility of anticoagulant, lifestyle

(anticoagulant monitoring needs), patient non-adherence with prior anticoagulant therapy, side-effects with prior anticoagulant therapy.

- which anticoagulant regimen was prescribed and start date
- clinical condition requiring anticoagulation (indication)
- Prior anticoagulation treatment
- Stroke and Bleeding risk factors
    - Congestive Heart Failure/Left Ventricular Dysfunction
    - TIA/Thromboembolism History
    - Previous History of Stroke
    - Vascular Disease History (previous MI, peripheral arterial disease or aortic plaque)
    - History of Hypertension
    - Current Hypertension
    - Uncontrolled BP, > 160mmhHg systolic at time of treatment initiation
    - Medication Usage Predisposing to Bleeding (Antiplatelet agents, NSAIDs
    - Labile INR (Unstable/high INRs)
    - Diabetes Mellitus
    - Alcohol Abuse or Excess†††††
    - Renal Disease (Dialysis, transplant, Cr >200 µmol/L)
    - Abnormal Liver Function (Cirrhosis, Bilirubin >2x Normal, AST/ALT/ALP >3x Normal)
    - Prior Major Bleeding or Predisposition to Bleeding

4.4.2.3 Patient 12 week end of observation questionnaire

For evaluable patients providing consent and for whom a completed index date questionnaire has been received by the DSRU, after at least 12 weeks of observation, a second questionnaire will be systematically generated to collect clinical information relevant to start of observation and any clinical events of medical interest (including serious adverse event reports [classified using the International Conference on Harmonisation definitions [36]] as recorded in the medical charts during the first 12 weeks of observation.

Data obtained from the 12-week end of observation questionnaire will include:

- Additional information on anticoagulation treatment regimen:

††††† Alcohol abuse/excess is classified as intake greater than current recommendation by the NHS guidelines of > 21 units for men or > 14 units for women per week

- details of prior use of oral and parenteral anticoagulant therapy (thienopyridines, aspirin, glycoprotein IIb/IIa inhibitors, heparins)
- If switching anticoagulant to either study drug: details of transition plan (both of prior anticoagulant and either study drug); Reasons for switching.
- Treatment regimen during the 12 weeks observation period (number of prescriptions issued (with dates, posology and duration) if known)
- Dates and reasons for changes in anticoagulant treatment regimen during 12 week observation period‡‡‡‡‡
- All relevant laboratory blood parameters during two-week observation period pre-index date and during 12 week observation where applicable (haemoglobin, platelet count, baseline clotting screen (PT, APTT, Fibrinogen Derived, D-Dimer) [*NB abnormalities would be reported as events*]
- If study drug stopped: date and reason for stopping, details of transition plan to alternative anticoagulant of study drug stopped; if required, details of reversal of anticoagulation therapy and management of bleeding complication.

- Recent (< 4 weeks prior to index date) and concomitant medications (at index or during treatment):
  - not recommended for concomitant use (including azole antimycotics [e.g. ketoconazole] and HIV protease inhibitors)
  - to be used with caution (including fluconazole, strong CYP3A4 inducers, P-gp inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, oral steroids, hormone and oral contraceptive therapy, platelet aggregation inhibitors or other antithrombotic agents)
- Medical history relevant for important potential, identified and special risks of interest (plus dates of first diagnosis/report). **For example:** past history of DVT/PE, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), other recent surgery within 3 months prior to index date, malignancy, pregnancy, family and/or personal history of congestive heart failure, diabetes mellitus, hypercholesterolaemia, peripheral arterial disease, COPD etc.)
- Specific information on renal function status at index date and any changes during 12 week observation period
- Specific information on hepatic disorders present at index date (cholestasis and jaundice, hepatic failure and associated disorders, hepatic fibrosis and cirrhosis and hepatic viral infections) and any recent abnormal liver function tests.

‡‡‡‡‡ for rivaroxaban only

- event reports including selected risks of interest (Table 4)
- cause and date of death (if died) in the first 12 weeks after starting treatment;
- reported pregnancies at start or during the first 12 weeks after starting treatment and outcome of birth.
- behaviours prior to and/or starting treatment (e.g. smoking, alcohol/substance misuse); treatment adherence

Table 4. Selected events of interest requiring further evaluation

Risk/Missing Information	Proposed data capture	Comment
IDENTIFIED, POTENTIAL AND SPECIAL RISKS AND OUTCOMES for targeted data collection on SCEM questionnaires		
Major bleeding episode (into a critical organ sites)	Targeted outcome questions on critical sites	Selected risk factors collected on SCEM questionnaire. Further data on severity, management and risk factors to be collected via follow-up.
Clinically relevant minor bleeding episodes	Targeted outcome question to specify details	Selected risk factors collected on SCEM questionnaire. Not for follow-up
Incident and recurrent thromboembolic complications (DVT, PE, Stroke)	Targeted outcome questions	Selected risk factors collected on SCEM questionnaire. Further data on symptoms, severity, management and risk factors to be collected via follow-up.
Overdose. accidental trauma and Reversal of anticoagulation therapy	Targeted outcome question	Events of overdose (dose > 50mg/day) and accidental trauma are those of clinical medical importance which require acute medical/surgical treatment (with or without) hospitalisation Further data to be collected via follow-up
Management of homeostasis	Targeted outcome question	Data on management of homeostasis in patients reported with events of surgery (elective or urgent) during the observation period will be collected via follow-up
Increased liver transaminases and Gamma-Glutamyl Transferase (GGT)	Targeted outcome question	Data on diagnosis of hepatic failure and where abnormal laboratory results indicate 3 X ULN relevant parameters will be collected via follow-up.
Concomitant use of contraindicated medications and medications to be used with caution	Targeted outcome question on other medications to gather duration and changes	Further data may be collected via follow-up
IMPORTANT MISSING INFORMATION for general surveillance		
Use during pregnancy and lactation	General event report	Further data to be collected via follow-up

4.4.2.4 Abridged 12 week end of observation questionnaire for GP

For each evaluable patient recorded as having been discharged from under the care of the specialist HCP to the care of their GP during the 12 week observation period, their GP will be contacted and invited to complete an abridged end of observation SCEM questionnaire which will gather information on clinical events of medical interest and serious adverse event reports [classified using the International Conference on Harmonisation definitions [36]] reported since date of discharge from secondary care up to end of the 12 week observation period, and recorded within primary care medical charts. Data obtained from this abridged 12 week SCEM questionnaire will include:

- Anticoagulant treatment regimen as prescribed in primary care
- event reports of selected risks of interest (Table 4)
- cause and date of death (if died);
- reported pregnancies and outcome of birth.
- date and reasons for stopping (if stopped) including switching
- any newly prescribed concomitant treatments

4.4.2.5 Follow-up Questionnaires

During the course of the study, selected outcomes of interest (arising from Section 2.2) may undergo further evaluation for aggregate assessment of drug- relatedness to inform on any unusual features/manifestations, relevant risk factors, clinical course and behaviours (see section 4.8). Where necessary, a supplementary follow-up questionnaire which is bespoke to the outcome of interest may gather additional relevant information where recorded within medical charts. [37]

With the exception of these enquiries for additional information on selected events, no further monitoring of patients for purposes of data collection will occur post the survey period. In accordance with Good Pharmacovigilance Practice (GVP) sections VI.C.1.2.1 and VI.C.2.2.2, [38] data will be analysed at aggregate level partially at the time of compiling the interim report (because all information may be available then) and at study completion. Such aggregate analyses can help formulate possible hypotheses which then require further analytic study. Because of the epidemiological nature of the design of this cohort study, any *conclusions* on drug-relatedness will be made on aggregate basis at study milestones, i.e. when the interim and final reports are written (see Section 4.9.2 on Communications).
If any other safety issues become apparent during the conduct of this study, additional events and/or event categories may be added to the list of events for follow up and this will be documented accordingly.

Specific events of interest for further evaluation*:*

1. Pregnancies: All reported pregnancies will be followed-up using a supplementary questionnaire to describe the outcome of pregnancy[§§§§§].

[§§§§§] Drug-relatedness assessments of abnormal birth outcomes are not conducted by the DSRU

2. Deaths: All reported deaths will be followed-up to try to establish the cause of death.

3. Events: Selected events of interest as defined in Table 4 may be followed-up for additional information on relevant risk factors, where insufficient information is provided on the questionnaire. The event of switching given as a reason for stopping rivaroxaban (although not defined in Table 4) will undergo further evaluation.

4. Adverse events: Other adverse events deemed of medical importance by the DSRU which are considered to be possible safety signals (either arising from literature reports post marketing, or subsequent to interim data analysis) may also be followed-up for additional information on relevant risk factors for signal strengthening purposes.

5. Adverse events: Events within the list of Rare and Iatrogenic Adverse Reactions (RAIDAR) compiled by the DSRU (Appendix 2) will be automatically followed up if a more likely alternative explanation for their occurrence is not given.

4.4.3 Methods to Maximise Questionnaire Response Rate

4.4.3.1 Patient 12 week end of observation questionnaire

A proportion of Specialist HCPs or GPs are likely to fail to submit these questionnaires. Methods to maximise response rates will include prompts from study facilitators by phone, email and personal contact and reminder questionnaires targeted at those who have not responded within one month of the date the initial questionnaire was sent.

4.4.3.2 Specific event follow-up questionnaires

A duplicate event follow-up questionnaire will be sent to specialist HCPs or GPs for the specific patient(s) for whom they have not responded to the initial follow-up questionnaire; within six weeks of the date the initial event follow-up questionnaire was sent. Specialist HCPs and GPs will be offered remuneration for each follow-up questionnaire that is completed and returned to the DSRU.

4.5 Data processing

Specialist HCP/ GP/patient identifiable information will be stored within a unique database. All original documents and individual correspondence from HCPs will be stored for 15 years at the DSRU, with considerable care taken to preserve patient confidentiality (see below).

4.5.1 Review of data

All returned questionnaires with clinical data will be coded onto the study database. Medically important adverse events that have been selected for follow-up will be coded as a priority. There will be a regular monthly review of both the number of patients identified and study questionnaires returned, processed, and classified as void. This will assist in determining the point at which the final cohort size will be achieved. Aggregate data will be reviewed at interim and end of study milestones.

4.5.2 Coding of data

Data on indications, exposure, relevant medical history and medication use plus events of interest will be coded directly from targeted closed format questions on the questionnaire (which reference Medical Dictionary for Regulatory Activities (MedDRA) terminology) and coded onto the bespoke study database. Other events reported on the questionnaires as free text will be coded onto this database using the DSRU Event Dictionary Doctor Summary Term synonym list that is mapped to MedDRA, in order to enable consistent reporting to be provided using MedDRA terminology.

Study specific coding procedures will facilitate consistency in coding the data. An SOP will be created upon development of the study specific SCEM database and will be maintained within the DSRU. Regular meetings of DSRU staff will be held to discuss study questionnaires that are difficult to code. A consensus opinion will be reached by medically qualified staff.

Methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific Data Management Plan (DMP) which will be constructed to assist database development and data analysis.

Completed questionnaires will be examined upon receipt for data completeness. Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the reported data may not be interpretable, or where the value

must be imputed to be missing because of data inconsistency or out-of-range results. The individual responsible for completing the questionnaire will be contacted to obtain the missing or correct information and data corrected when possible.

The degree of data completeness will be summarized at interim stage. The distribution of observed variables for patients with missing data will be compared to patients with complete data to gain insight into whether there is any non-random systematic missing information. The most appropriate method to handle missing data for final analysis will be determined by the Project Steering committee at Interim stage.

4.5.3 Confidentiality procedures

All DSRU staff sign confidentiality agreements and the DSRU is registered with the office of the Data Protection Registrar (Registration No. Z5438861).

DSRU information security policies are in place to preserve the confidentiality, integrity and availability of the organisation's systems and data. These include ensuring the premises provides suitable physical and environmental security, all DSRU equipment is secure and protected against malicious software, the network can only be accessed by authorised DSRU staff, telecommunication lines to the DSRU premises are protected from interception by being routed overhead or underground and personal receive training regarding security awareness.

All original documents, individual correspondence from specialist HCPs, will be stored for 15 years at the DSRU, with considerable care taken to preserve the confidentiality of data. The DSRU databases are well protected. To ensure patient anonymity, the names and addresses of patients will be deleted from the DSRU database at an appropriate time point (provisionally this is at datalock or earlier if patients have provided informed notification that they wish to withdraw from the study, but the DSRU will request an extension to this to comply with CHMP requirements). Until this time, only appointed staff would have access to such data.

4.6 Quality Assurance

Good clinical data management is a high priority at the DSRU. A number of strategies exist to minimise biased event monitoring study results. The DSRU has a set of rules and processes associated with the conduct of pharmacoepidemiological studies. Data quality is assured

through a number of methods based on error-prevention, data monitoring, data cleaning and documentation. These include:

- Operator training;
- Vigilance of operators at the various stages of processing,
- On screen validation during data entry,
- Adoption of and adherence to study-specific data coding conventions,
- Coding review meetings,
- Code list and algorithms
- Double entry (100% of questionnaires), error reporting and correction of discrepancies between the entries by quality assurance staff
- Coding of questionnaires are randomly reviewed by a quality assurance assessor.
- Routine data cleaning to screen for errors, missing values and extreme values and diagnose their cause; this being supported by bespoke software with objective, standardised logical checks and undertaken by the DSRU data manager or allocated staff.
- Relevant maintenance of reference tables, e.g., Event Dictionary
- Pilot testing of study documentation

4.7 Data analysis

4.7.1 Cohort accrual, the type of specialist HCP responsible for, the setting of initiation of treatment, specialist HCP preference factors and non-clinical reasons for prescribing

The following relates to Section 2.2.2 Secondary objectives (i) and (ii). Data on specialist HCP response rates will be presented, as will data on prescriber demography, type, setting and institution, specialist HCP preference factors and non-clinical reasons for prescribing. These data will be used to inform on cohort accrual and study timelines to target sample size.

Cohort accrual will be summarised with description of losses to follow-up and withdrawals. [39] Patients who decline to participate will be compared to those who provide consent (through use of data collected on the invitation log) in terms of demographic variables to assess potential for selection bias through non-participation. Similarly, patients who are lost to the study because of withdrawal of consent, or because of attrition will be compared to those who remain in the study to examine whether there are any systematic differences in demographic or treatment variables which may affect internal validity or generalisability.

4.7.2 To estimate the cumulative incidence of the important identified risk of haemorrhage for rivaroxaban.

The following relates to Section 2.2.1 primary objective (i) for rivaroxaban only and relates to haemorrhage within gastrointestinal and urogenital organ sites (which meets the criteria for a major bleed) and all intracranial sites (as defined in Table 2)..

For the three organ sites specified in the primary outcome, each of the individual components of the major bleeding criteria (a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, or a fatal outcome - as per table 2) will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event. The cumulative incidence (risk) of the primary outcomes reported during treatment within the 12 week observation period will be explored by estimating the cumulative incidence of incident reports (plus 95% CI) and cumulative hazard rates (plus 95%CI) of incident events over time. For purposes of this analysis the denominator (person-period at risk) is defined as the 12 week observation period (i.e., the time from the date the first prescription was issued for rivaroxaban (treatment index date) until the date of stopping (+ 2 days) or at 12 weeks if patient did not stop, whichever occurs first). The numerator will comprise of reports of incident major bleeding events during that 12 week observation period. These which have been adjudicated by expert review (using all available information from SCEM questionnaires, follow-up and any additional documentation). Where such information reveals that the event was misreported, that patient will excluded as a case from the analysis, but contribute person-time exposed.

The cumulative incidence will be calculated according to the formula:

$$\frac{\text{Total number of new cases during 12 week observation period}}{\text{Population initially at risk}} \times 100$$

If the observed cumulative incidence from the SCEM study falls within the range expected as set by the precision limits of cumulative incidence from clinical trial data, then the null hypothesis (of no difference) will not be rejected. Cumulative hazard rate methods account for truncation of exposure time and censoring; for these analyses the exposure time would be censored at the time of the first event. Kaplan-Meier plots will be presented to describe time-to event as well as smoothed hazard plots to describe how the baseline risk of an event

changes over time. Estimates of the hazard function will also be modelled to determine whether the baseline hazard (risk) of the event increases or decreases with time. A constant hazard over time may be consistent with a background (not caused by the drug) event rate, whereas a non-constant hazard over time may be an indicator of a drug-event relationship. The null hypothesis that the hazard rate of the selected event in patients prescribed rivaroxaban will be constant during the 12 week period following the start of treatment will be tested by fitting a parametric time to event model (e.g. Weibull). Such models have a shape parameter that indicates whether the hazard is significantly increasing or decreasing over time. At least five reports of an event are deemed necessary for modelling purposes.*******

Several sensitivity analyses will be performed: In one, observation start date will be imputed to be the same as the diagnosis date (i.e the index date will be shifted backwards in time) for those patients for whom a lag period between diagnosis and receiving rivaroxaban treatment was reported. The application of time-varying covariates methodology will enable examination of the impact of any transition from other treatments given as part of initial standard care on the results. In addition, since the primary analysis will be run only to include confirmed cases of incident major bleeding, it will be necessary to explore the reasons for exclusion of incomplete cases and examine their impact on the estimated measure of frequency.

Where possible, data will be stratified according to relevant strong risk factors (e.g. gender, age ($\leq$60, 60-74, $\geq$75 years), indication and past history of haemorrhage or VTE) and stratum-specific incidence rates examined.

Graphs of cumulative counts of events of interest, by month over the study period, will be examined for possible change in reporting over calendar time.

4.7.3. To describe the health profile of patients at index date prescribed treatment with rivaroxaban in the secondary care hospital setting and the treatment programme they received to advance the understanding of the rivaroxaban patient population in actual clinical practice in relation to the contextual cohort.

******* *e.g. when the shape parameter (p) for the Weibull model is equal to one, the hazard is estimated to be constant over time, if p is greater than one the hazard is increasing, if p is less than one the hazard is decreasing. The hazard function will be determined as non-constant if the 95% CI excludes the value one*

The following relates to Section 2.2.2 secondary objective (ii). Valid cohort demography (patient self-reported: age, gender, ethnicity, socioeconomic index) will be presented separately for both rivaroxaban and the contextual cohort, as reported at index date using all available information from questionnaires (completed by patient and specialist HCP). Other patient self-reported general health factors [BMI, weight, height, smoking and alcohol use] and indication-related characteristics [primary (and secondary if provided) diagnosis/decision, date and duration since first ever recorded; stroke and reported bleeding risk factors; pattern of most recent INR/APTT levels if switching from prior anticoagulant]; anticoagulant treatment initiation programme by specialist HCP (index date, dose and frequency) and non-clinical prescribing reasons. A synopsis of pre-index and concurrent relevant morbidities and medication use will also be provided.

For rivaroxaban cohort only, patient subgroups of special interest (Table 5 – 'off-label' use defined as arising from contraindications and those for which: a) precautions for use are recommended; b) appropriate clinical monitoring is recommended; c) limited information is available; and d) selected concomitant drug use) will be summarised in order to inform on real-life use of rivaroxaban. The proportion of patients within each special population sub-group prescribed rivaroxaban who had *one or more* relevant characteristics/conditions/co-prescribed medications at index date will also be summarised within each indicator group by simple aggregation of counts (Table 5).

Further stratification within-cohort by calendar period *may* also be undertaken to identify any cohort effects or trends that may be emerging.

Table 5. Special population Indicators of Use for Rivaroxaban

5a) Indicators of Contraindicated Use *(Patients can have up to 5 indicators)*
Treatment for medical indications other than licensed indications
Clinically significant active bleeding
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
Use in pregnancy and lactation
Hypersensitivity to the active substance or to any of the excipients
5b) Indicators of Use with Special Warnings or Precautions *(Patients can have up to 11 indicators)*
Patients with liver cirrhosis with moderate hepatic impairment (classified as Child Pugh B), not associated with coagulopathy
Severe renal impairment (patients with creatinine clearance < 30 ml/min)
Moderate renal impairment (patients with creatinine clearance 30-49 ml/min)
Congenital or acquired bleeding disorders
Uncontrolled severe arterial hypertension
Active ulcerative gastrointestinal disease
Recent gastrointestinal ulcerations
Vascular retinopathy
Recent intracranial or intracerebral haemorrhage
Intraspinal or intracerebral vascular abnormalities
Recent brain, spinal or ophthalmological surgery.
5c). Indicators of Use in Patients with Limited Information *(Patients can have up to 1 indicators)*
Patients with AF and a prosthetic heart valve
Children aged ≤ 15 years
5d) Indicators of Use with Potential Drug-Drug Interactions *(Patients can have up to 4 indicators)*
Concomitant systemic treatment with azole-antimycotics, e.g ketoconazole or HIV protease inhibitors
Concomitant treatment with CYP3A4 inhibitors/inducers or P-gp inhibitors
Concomitant treatment with other anticoagulants
Concomitant use with NSAIDs and platelet aggregation inhibitors

4.7.4 To describe changes of health profile of patients, assessment of adherence; number of indication related episodes and duration, plus any alterations of the treatment programme during the 12 week observation period.

The following relates to Section 2.2.2 secondary objective (iii) Status of indication-related characteristics (alteration of diagnosis, stroke ($CHADS_{2/}$ CHA_2DS_2-VASc) and bleeding risk score (HAS BLED) if available) will be summarised, plus pattern of anticoagulant treatment adherence at the end of the 12 week observation period (as estimated from Medication Possession Ratio[††††††]) will be summarised. The frequency and reasons for attendance to clinics for review and management of anticoagulation and/or acute hospitalisations (including hospital referrals) will also be summarised, where reported. Alterations in treatment programme (change in dose, other drugs) will be described, as will any reason(s) for stopping treatment (including switching) and transition plans to other anticoagulants.

Changes in these indication-related characteristics and treatment details will be examined by comparing values at index and at 12 weeks post index date. Exploratory analysis may include data mining and descriptive measures for describing alterations in treatment programme.

The number of pregnancies, trimester of first exposure and details of births, terminations and miscarriages will be presented. The number of deaths (as recorded in medical charts) in the total cohort for each month of exposure will be calculated. Causes of death will also be described by system-organ class.

Sensitivity analyses will examine any under-reporting using data provided from the patients GP.

[††††††] For this study, MPR will be defined as: $\frac{\text{No. days supply held during treatment}}{\text{No. days supply expected during treatment}} \times 100$

Where no. days held will be calculated from information derived from 12 week questionnaire on number of prescriptions and average treatment length of prescriptions (usually given in 7, 14,28,56 day repeats); no. days supply expected will assume chronic use from start to end of study observation or treatment stop date (if stopped)

4.7.5 To quantify the incidence risk and rate of events reported in the 12 week observation period in both the rivaroxaban and contextual cohort and in patient subgroups of special interest.

The following relates to Section 2.2.2 secondary objectives (i) and (iv) regarding a) major bleeding outcomes as specified in the primary objective for the contextual cohort, b) other major or non-major clinically relevant bleeding outcomes not specified in the primary objectives , c) thromboembolism (recurrent and incident) and d) any other events reported in the 12 week observation period .

For major bleeding events not specified in the primary outcome, each of the individual components of the major bleeding criteria (a fall in haemoglobin of 2 g/dL or more, or a transfusion of 2 or more units of packed red blood cells or whole blood, or a fatal outcome - as per table 2) will be summarised. Where an individual has one or more criterion for an individual organ site of interest, this will also be summarised – in such individuals the first report will be regarded as the incident event.

For clinically relevant non-major bleeding events, each of the individual associated components (as per table 2 such as requiring medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study drug treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life) will be summarised. Where an individual has one or more criterion for a clinically relevant non-major bleeding event, this will also be summarised – in such individuals the first event report will be regarded as the incident event.

Analysis of event data for purposes of signal detection includes exploring overall risk and rate for the observation period and time to onset profiles. The methodology provides a numerator (the number of reports of an event) and a denominator (person-time at risk), both collected within a known time frame. This allows for the calculation of crude risks (percent of total valid cohort exposed) and rates (Incidence Densities-ID; person-time incidence rates) for each event separately. Each event may be reported in response to a closed question (for example information on each individual major and/or clinically relevant non-major bleeding risk component), or as free text in response to open questions on the data collection forms. Such analyses will be performed using 'Higher-level' event terms from the MedDRA dictionary where possible. The risk profile of the overall cohorts and sub-group of interest

(based on index date characteristics, including whether anticoagulant naïve, rivaroxaban naive or past (other anticoagulant user) will be described by presenting summary tabulations (by rank) of counts and incidence risk of reported events, and crude event rates (IDs).

Calculating and ranking crude ID rates is one of a number of standard quantitative evaluations used in event monitoring methodology for signal generation purposes as part of initial inspection of all event data for general safety surveillance. It is used as a means of alerting early potential signals as priorities for further evaluation. Medical judgment however is also part of this evaluation and prioritization process. Crude Incidence Densities (ID) [‡‡‡‡‡‡]can be calculated by week in order to quantify rates of events. IDs will be calculated, for each given time period (t), for all events reported in patients who continue to take rivaroxaban for a given time period, or for whom the date of stopping is known. Only the first report of an event in an individual patient is used in the calculation of IDs. They are usually expressed as the number of first reports of an event per 1000 patient-weeks. This assumes the pattern of use is continuous. The numerator will be the first reports of events reported as occurring after the index date and during treatment.[§§§§§§] For this study, IDs will be calculated for each event for each week as follows:

$$ID_t = \frac{\text{Number of first reports of an event during treatment for period t} \times 1000}{\text{Number of patient-weeks of treatment for period t}}$$

Thus, $$ID_t = \frac{N_t \times 1000}{D_t}$$

where: N_t = Number of first reports of an event during treatment for period t,

and D_t = Number of patient-days of treatment for period t / 7

IDs will also be calculated for each event for all 12 weeks during treatment combined (ID_A), and the first week after stopping (ID_{SW1}) if patient stopped (and where patients are recorded as remaining on treatment for at least 1 week) after index date.

[‡‡‡‡‡‡] It should be noted such quantification of rate does not only reflect the rate attributable to the drug but also reflects the background rate in the general population and rate attributable to other factors such as age or other disease risk factors

[§§§§§§] Ideally, the exposure time would be censored at the time of the first event. However, since there are a large number of health outcomes of interest and the censoring would be different for each outcome, the denominator for the crude ID will not initially include censoring. If an elevated crude ID is identified in this monitoring analysis, a subsequent analysis with appropriately censored denominator will be performed for that outcome.

Sensitivity analyses will examine any under-reporting by including events of interest recorded in primary care medical charts and confirmed on follow-up for those patients discharged to primary care, during the 12 week observation period.

As IDs for the overall cohort may sometimes mask significant signals in specific risk groups, the subgroups defined by specific characteristics (e.g. previous history of VTE or haemorrhage, previous/concurrent use of selected medications, off-label indication groups, rivaroxaban naïve or past user) will have IDs calculated and compared according to strata for relevant events, where appropriate.

It is possible to explore the time taken for an event of interest using parametric time to event models (e.g. Weibull) as described previously, thus providing an additional tool for signal generation purposes. This approach will be explored for events of interest, where counts ≥ 5. If undertaken, a sensitivity analysis will be performed to include in the numerator events reported within 7 days of stopping, and extend the denominator by 7 days

4.7.6 To characterise differences in prevalence of prognostic factors and clinical risk factors for haemorrhage associated with rivaroxaban in comparison with contextual cohort as reported during the first 12 weeks after starting treatment in routine secondary care hospital setting in UK.

This relates to Section 2.2.1 secondary objective (v), the aim of which is to explore the effect of important predictors (prognostics characteristics, selected relevant risk factors and oral anticoagulant on the primary outcomes of interest (haemorrhage), **only if sufficient numbers of cases of primary outcome are reported**. The effect of physician anticoagulant prescribing preference factors (type of novel anticoagulants prescribed in previous calendar month; proportion of novel anticoagulant use of all anticoagulants prescribed in previous calendar month), medical education, setting and institution will be explored as a suitable conditioning (instrumental) variable for modelling..[40] Since, data are likely to be hierarchical the application of a multilevel model for discrete response data will be considered. Odds ratios and 95% confidence intervals will be calculated.

4.7.7 To describe clinical features and management of cases of overdose, major bleeding, VTE events indicating failure of anticoagulation and management of homeostasis in

patients undertaking surgery (elective or urgent) reported in the first 12 weeks after treatment initiation in the cohort exposed to rivaroxaban.

The following relates to Section 2.2.3 exploratory objective (ii) . A qualitative assessment of these cases will include evaluation of patient demographic characteristics, treatment details, the detection and clinical features and management of events of interest, resolution, relevant investigations prior to and during therapy, the patient's relevant medical history and concurrent medication and any sequelae. Data will be derived from the SCEM and follow up questionnaires sent to gather other relevant essential information for construction of a case-series summary descriptive table.

4.7.8 Multiple comparison adjustments

The methods of signal surveillance require a large number of multiple comparisons on adverse events, which involve inferring statistical significance on multiple *p*-values. To control for an excess of false positive signals, suitable multiple comparison adjustments will be made with the false discovery rate (FDR) approach. [41] The Simes method [42;43] in addition to the double FDR method [41] will be implemented to maintain the false discovery rate at the acceptable 10% level for all statistical tests. Such approaches would allow for a balance between false positive and false negative signals.

4.8 Aggregate Assessment of Drug- Relatedness of Selected Events

As described previously (section 4.4.1.3) selected events of interest (Table 4) that require further characterisation and evaluation may be followed-up via a questionnaire sent to the responsible specialist HCP or patient's GP seeking further information. The information received at follow-up for events of medical significance or those which require further clarification will facilitate further evaluation at the aggregate level , including collective assessment of drug-relatedness, by experienced research staff at the DSRU (two qualified members of staff, independently, with a third adjudicator if necessary). The aim of the collective drug-relatedness assessment for groups of events during the analysis of the interim and final reports, is to put events in context regarding temporality co-morbidity, pre-existing disease and concomitant medications. This aggregate assessment of event data occurs at interim or final report for cases for which all requested information (i.e. index date questionnaire, 12 week end of observation questionnaire, and follow-up questionnaire if applicable) has been received. In the process of aggregate assessment of event data, the

application of elements of the Austin Bradford Hill criteria , when the necessary information is available and the use of the method is considered appropriate, will be used (see Box 1) .[44]

Box 1. Points for consideration in collective evaluation of reported events

- *The distribution of time to onset (temporal relationship);*
- *The principle clinical and pathological characteristics of the group of events;*
- *The pharmacological plausibility based on previous knowledge of the drug and the therapeutic class if appropriate;*
- *Similar reports in medical literature*
- *patient's clinical characteristics, including:*

- previous medical history, such as history of drug allergies, presence of renal or hepatic impairment, etc.

-concomitant medications or medications taken prior to and during treatment;

- *Management and remedial action;*

The collective drug-relatedness of selected groups of events of interest will be categorised in terms of proportions of reports assessed within the following four categories: 1) probable[*******], 2) possible[†††††††], 3) unlikely[‡‡‡‡‡‡‡], and 4) not assessable[§§§§§§§]. [45]

4.9 Data Monitoring

4.9.1 Project Steering Committee

A Project Steering Committee (PSC) will be set up to be comprised of the study investigators and other experts. The role of the PSC will be to oversee the smooth running of the project and provide scientific, statistical and technical advice when needed and will meet at regular intervals (3 to 12 monthly depending on the stage of the study, either in person or by teleconference).

[*******] Events are assessed as 'probable' if the event is well defined clinically and pathologically, if there is a reasonable time sequence, if it is more likely to be attributed to the study drug rather than to a concurrent disease or concomitant medication, if there is a positive dechallenge, rechallenge or response to dose increase, and if there are other supporting criteria (e.g. on the basis of lab tests or histological findings).

[†††††††] Events are assessed as 'possible' if the event has a reasonable clinical and pathological definition, if there is a reasonable time sequence, if it could also be explained by concurrent disease or concomitant medication, but dechallenge, rechallenge and confirmatory investigations are inconclusive or not fully available. Medical judgement will be necessary in some cases.

[‡‡‡‡‡‡‡] Events are assessed as unlikely if the event had a temporal relationship to the study drug administration that made a causal relationship improbable, or if concurrent disease or concomitant medication provided a far more plausible explanation.

[§§§§§§§] Events are unassessable if insufficient information about the event has been provided and an appropriate evaluation is therefore not possible.

The PSC is broadly analogous to a Safety Monitoring Committee or Review Board, but the purpose may be slightly different such that the PSC includes investigators and also oversees the effective progress of the study. The first PSC meeting will orientate the project team members and establish the logistics for specialist and patient recruitment and confirm patient inclusion criteria. Subsequent PSC meetings will clarify the understanding of the ongoing project requirements, monitor progress through assessment of data within the interim reports [specialist/cohort accrual rates, preliminary analyses of individual variable responses on questionnaires], consider any additional proposed inclusion criteria, and act as a forum to review and discuss any queries.

4.9.2 Communications

Progress reports (relevant to specialist and patient cohort accrual) will be produced in time for inclusion in the scheduled Periodic Safety Update Reports for the product (i.e., every six months for the first two years after launch and then annually thereafter) or regular updates of the RMP for as long as the study continues. Examination of aggregate event data will be limited to one interim report based on the evaluable study cohort achieved at approximately 18 months post date of first patient recruited, and a detailed final report based on the evaluable study cohort achieved at approximately 36 months post date of first patient recruited. It is anticipated that the final cohort for analysis will be comprised of 3400 evaluable patients with relevant indications. However the final sample size achieved within this timeframe will be governed by application of NICE guidance (which can vary) between secondary care trusts and managed entry, therefore the possibility of a requirement to extend the study period must be acknowledged.

4.9.3 Adverse event /reaction reporting

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This registry-based, observational, non-interventional cohort study is based on secondary use of data, therefore adverse reactions reporting is not required. Reports of adverse events/reactions will be summarised in the study report, where applicable. The DSRU shall, on an ongoing basis, notify the MAH when they consider, based on their evaluation, that any issues or matters of interest relating to the Study or its outcomes are of importance and shall provide the MAH with related results of the study and analyses thereof.

Since the clinicians are prescribing a licensed product, they will be reminded in the study documentation that it is their responsibility to report any suspected adverse reactions (including serious******** adverse drug reactions) to the company and/or to the MHRA (using Yellow Cards) as they would normally do in their practice in support of routine pharmacovigilance. In cases where the DSRU receives, by mistake, such reports it will forward them to the MHRA and/or the MAH as appropriate.

5.0 STRENGTHS AND LIMITATIONS

5.1. Strengths

- The observational and inclusive design allows for the surveillance of a diverse patient population under the care of specialist HCP, particularly those that are more complex in terms of underlying disease, co-morbidities and concomitant medications that would not have been included in clinical trials, and also would not be comparable to the general disease population. Thus error introduced through selection based on disease severity or type will be minimised; there are no specific exclusion criteria. The approach also allows for surveillance of rivaroxaban when used off-label.
- The prescribing of relevant pharmacological therapy should not be affected because of participation in this study therefore the observational non-interventional nature of the study design is maintained.
- Data is collected on large numbers of rivaroxaban and warfarin users in conditions of routine clinical practice.
- Special populations can be characterised
- Time-dependent effects can be examined .This method is prospective and thus will enable more reliable examination of exposures in relation to outcomes.
- By obtaining patient consent, additional information from medical charts from other clinical specialities may be examined for selected outcomes.
- Extension to monitor long-term safety is possible.

******** **Definition of Serious Adverse Event**

"Serious Adverse Event means an adverse event which is fatal or life-threatening, results in persistent or significant disability, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

- The DSRU has established networks of specialists in the UK to conduct such studies.

5.2 Limitations

- Possible delay in new user cohort accrual if adoption by secondary care hospital trusts and specialists is low.
- Since this is an observational epidemiological study, we recognise several potential sources of bias. The most important is selection bias and the possibility that the cohorts will not be representative of the general population for whom anticoagulation is clinically desirable. Because of the prospective nature of patient recruitment, bias in recruitment may be introduced by some participating specialist HCPs through awareness of some form of remuneration (regardless of how and when payment is made). This study does not look at the comparative early safety profile of rivaroxaban in the context of initiations of other novel anticoagulants; therefore the extent of selection bias cannot be established in regard to those treatments. However the same number of patients treated with warfarin for similar indications will be collected to explore factors which may contribute to selection bias. Furthermore, the characteristics of patients providing consent to those who do not will be compared in order to identify possible systematic differences between such patients.
- Knowledge of which patients will be participating may affect the non-interventional nature of observational research. Exclusion of patients initiated on treatment between date of market launch and study start may also add to selection bias. Nevertheless patient identification (case ascertainment) is likely to be more complete than through retrospective methodology; this may also minimise bias introduced by non-participation of patients. It is also possible that specialist HCPs who participate in the study will be a self-selected group, but we do not believe that this selection bias will affect the types or number of events experienced and reported by a patient after treatment has been initiated. An instrumental variable reflecting physician prescribing preference will be explored to control for unmeasured confounding possibly associated with treatment decisions.
- Confounding by indication is a form of selection bias where the disease that forms the indication being treated (irrespective of severity) is not only associated with treatment but also an independent risk factor for selected outcomes (events of interest) in patients not exposed to antithrombotic agents. This needs to be examined since such channelling may result in apparent association of increased risk of such events in this population. It may be introduced through prescribing of treatment based on certain

characteristics of a patient. For this study, patients for whom prior alternative treatment was poorly tolerated or ineffective may be selectively prescribed the new treatment.

- Confounding by severity is possible and needs to be accounted for.
- Under- and mis- reporting of outcomes is possible; specialist HCPs' notes may be incomplete with regard to medical history and non-cardiovascular related outcomes of interest associated with current treatment. The two-phase data capture approach could facilitate compliance with data reporting as well as spreading workload for specialist HCPs. By obtaining patient consent at the start of treatment to facilitate communication with the Patient's GP and access to primary medical charts, under ascertainment of outcomes can be minimised. In contrast, overreporting and overrecording of health related events in the period following the administration of the index questionnaire are possible due to increased specialist HCPs' attention to special populations of interest (e.g. SPAF) as detailed in the questionnaire, however since information is being abstracted from medical charts such bias is unlikely. Where similar information is obtained from primary care medical charts by GPs who were not involved in treatment initiation, a sensitivity analysis may inform on the impact of such bias, if it exists.
- Regarding the definition of bleeding, in this study case definitions are based on acceptable agreed clinical standards and aim to address specific regulatory questions in the context of the risk management plan for the product.
- Immortal time bias is possible arising from misclassification of exposure to the study OAC.
- With this patient population, patient attrition and loss to follow-up may introduce selection bias, however, the relatively short period of observation should mitigate this possibility at least to some extent.
- Misclassification bias will be minimised by well defined outcome and follow-up of medically important events. Patients with selected events of interest will be followed-up with regard to co-prescribed medicines and concurrent illness. Events that represent features of the respective indications will be taken into account when signals of potential ADRs to rivaroxaban are investigated (i.e., confounding by indication).
- Time bias may also become an issue if the study collection period, and thus the observation period, is extended because of low prescribing rates.
- Furthermore unidentified poor adherence may also lead to misclassification of exposure. However, as with many observational studies, the degree of patient

compliance in taking the prescribed medication cannot be ascertained. Whilst it is not possible to be sure the patient used the medication, it is almost certain that the patient received it since starting treatment is required for study participation.

6.0 STUDY SPONSORSHIP

This study is being undertaken by the DSRU as part of the Risk Management Plan for the product at the request of the Committee for Medicinal Products for Human Use (CHMP). The Drug Safety Research Trust is a registered independent charity (No, 327206) operating in association with the University of Portsmouth and is the sponsor of the study. For this study, the DSRU (the academic sponsor) receives support from Bayer.

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Appendix 1. UK SPC for rivaroxaban

Bayer plc

Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA
Telephone: +44 (0)1635 563 000
Fax: +44 (0)1635 563 393
WWW: http://www.bayer.co.uk

Summary of Product Characteristics last updated on the eMC: 18/06/2012

Xarelto 10 mg film-coated tablets

1. Name of the medicinal product

Xarelto▼ 10 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 10 mg rivaroxaban.

Excipients with known effect:

Each film-coated tablet contains 27.9 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet).

Light red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "10" and a triangle on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

4.2 Posology and method of administration

Posology

The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

• For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.

• For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take Xarelto immediately and then continue the following day with once daily intake as before.

Converting from Vitamin K Antagonists (VKA) to Xarelto

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

Converting from Xarelto to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

Converting from parenteral anticoagulants to Xarelto

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Xarelto to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

Elderly population

No dose adjustment (see section 5.2).

Body weight

No dose adjustment (see section 5.2).

Gender

No dose adjustment (see section 5.2).

Paediatric population

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

Method of administration

For oral use. Xarelto can be taken with or without food (see section 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haemorrhagic risk

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

• congenital or acquired bleeding disorders

• uncontrolled severe arterial hypertension

• active ulcerative gastrointestinal disease

• recent gastrointestinal ulcerations

• vascular retinopathy

• recent intracranial or intracerebral haemorrhage

• intraspinal or intracerebral vascular abnormalities

• recent brain, spinal or ophthalmological surgery

• bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, rivaroxaban is not recommended in these patients.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase is not considered

clinically relevant.

Erythromycin (500 mg three times a day) which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

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

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

4.6 Pregnancy and lactation

Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies

Indication	**Number of patients***	**Maximum daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the

patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common (≥ 1/100 to < 1/10)

uncommon (≥ 1/1,000 to < 1/100)

rare (≥ 1/10,000 to < 1/1,000)

Not known: cannot be estimated from the available data.

Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery *(VTE-P),* treatment of DVT and prevention of recurrent DVT and PE *(DVT-T),* and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation *(SPAF)*)

Common	Uncommon	Rare	Not Known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
Tachycardia			
Vascular disorders			
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Haemoptysis		
Gastrointestinal disorders			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal	Dry mouth		

and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]			
Hepatobiliary disorders			
	Hepatic function abnormal	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B])	Renal impairment (incl. blood creatinine increased, blood urea increased)[A]		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise), localised oedema[A]		
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

*) These reactions ocurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for

Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15s).

The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

Clinical efficacy and safety

Appendix 1. UK SPC for rivaroxaban

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of VTE, i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme.

Rivaroxaban 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.

In all three phase III studies (see table 3), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non fatal PE and death) and major VTE (proximal DVT, non fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

Table 3: Efficacy and safety results from phase III clinical studies

	RECORD 1			RECORD 2			RECORD 3		
Study Population	4,541 patients undergoing total hip replacement surgery			2,509 patients undergoing total hip replacement surgery			2,531 patients undergoing total knee replacement surgery		
Treatment dose and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
Total VTE	18 (1.1 %)	58 (3.7 %)	< 0.001	17 (2.0 %)	81 (9.3 %)	< 0.001	79 (9.6 %)	166 (18.9 %)	< 0.001
Major VTE	4 (0.2 %)	33 (2.0 %)	< 0.001	6 (0.6 %)	49 (5.1 %)	< 0.001	9 (1.0 %)	24 (2.6 %)	0.01
Sympto-matic VTE	6 (0.4 %)	11 (0.7 %)		3 (0.4 %)	15 (1.7 %)		8 (1.0 %)	24 (2.7 %)	
Major bleedings	6 (0.3 %)	2 (0.1 %)		1 (0.1 %)	1 (0.1 %)		7 (0.6 %)	6 (0.5 %)	

The analysis of the pooled results of the phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. Rivaroxaban 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from the day of surgery and the following day when variability in exposure is high (70 %).

Appendix 1. UK SPC for rivaroxaban

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro*investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

Inter-ethnic differences

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7 - 273) and 14 (4 - 51) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E_{max}model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline Factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal 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.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate

Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters in cartons of 5, 10 or 30 tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

Bayer Pharma AG

13342 Berlin

Germany

8. Marketing authorisation number(s)

EU/1/08/472/001-010

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30 September 2008

10. Date of revision of the text

05/2012

Appendix 1. UK SPC for rivaroxaban

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

Distributed in the United Kingdom by:

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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 18/06/2012

Xarelto 15mg film-coated tablets

1. Name of the medicinal product

Xarelto▼ 15 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 15 mg rivaroxaban.

Excipients with known effect:

Each 15 mg film-coated tablet contains 25.4 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet).

Red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "15" and a triangle on the other side.

Appendix 1. UK SPC for rivaroxaban

4. Clinical particulars

4.1 Therapeutic indications

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.

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

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of DVT and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1 - 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Xarelto

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is ≤ 3.0.

For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

Appendix 1. UK SPC for rivaroxaban

Converting from Xarelto to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

Converting from parenteral anticoagulants to Xarelto

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Xarelto to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

Elderly population

No dose adjustment (see section 5.2).

Body weight

No dose adjustment (see section 5.2).

Gender

No dose adjustment (see section 5.2).

Appendix 1. UK SPC for rivaroxaban

Paediatric population

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

Method of administration

For oral use. The tablets are to be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors

Appendix 1. UK SPC for rivaroxaban

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

• congenital or acquired bleeding disorders

• uncontrolled severe arterial hypertension

• active ulcerative gastrointestinal disease

• recent gastrointestinal ulcerations

• vascular retinopathy

• recent intracranial or intracerebral haemorrhage

• intraspinal or intracerebral vascular abnormalities

• recent brain, spinal or ophthalmological surgery

• bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances

are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

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

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin,

carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

4.6 fertility, pregnancy and breast feeding

Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies

Indication	**Number of patients***	**Maximum daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

Appendix 1. UK SPC for rivaroxaban

*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common (≥ 1/100 to < 1/10)

uncommon (≥ 1/1,000 to < 1/100)

rare (≥ 1/10,000 to < 1/1,000)

Not known: cannot be estimated from the available data.

Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery *(VTE-P),* treatment of DVT and prevention of recurrent DVT and PE *(DVT-T),* and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation *(SPAF)*)

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
Tachycardia			
Vascular disorders			
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Haemoptysis		
Gastrointestinal disorders			

Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic function abnormal	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B])	Renal impairment (incl. blood creatinine increased, blood urea increased)[A]		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise), localised oedema[A]		
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A] , increased LDH[A] , increased lipase[A] , increased amylase[A] , increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

*) These reactions ocurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina

pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 16 to 33 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 s .

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for

PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine . However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

Clinical efficacy and safety

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; P<0.001 for non-inferiority) Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

Table 3: Efficacy results from phase III ROCKET AF

•	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value, test for superiority
Stroke and non-CNS systemic embolism	269 (2.12%)	306 (2.42%)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572	609	0.94

	(4.51%)	(4.81%)	(0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and Myocardial infaction	659 (5.24%)	709 (5.65%)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99%)	281 (2.22%)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16%)	27 (0.21%)	0.74 (0.42 - 1.32) 0.308
Myocardial infaction	130 (1.02%)	142 (1.11%)	0.91 (0.72 - 1.16) 0.464

Table 4: Safety results from phase III ROCKET AF

• Study population	• Patients with non-valvular atrial fibrillation[a]		
Treatment dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value
Major and non-major clinically relevant bleeding events	1,475 (14.91%)	1,449 (14.52%)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60%)	386 (3.45%)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24%)	55 (0.48%)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82%)	133 (1.18%)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49%)	84 (0.74%)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305	254	1.22 (1.03 - 1.44)

	(2.77%)	(2.26%)	0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65%)	149 (1.32%)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80%)	1,151 (11.37%)	1.04 (0.96 - 1.13) 0.345
All cause mortality	208 (1.87%)	250 (2.21%)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment

* Nominally significant

Treatment of DVT and prevention of recurrent DVT and PE

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall combined treatment duration in both studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (≥ 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p < 0.0001 (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI= 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2 - 3) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI, 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

In the Einstein Extension study (see Table 6) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

Appendix 1. UK SPC for rivaroxaban

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 -- 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e.15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

Table 5: Efficacy and safety results from phase III Einstein DVT

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto[a] 3, 6 or 12 months N=1,731	Enoxaparin/VKA[b] 3, 6 or 12 months N=1,718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days followed by VKA

***** $p < 0.0001$ (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

Table 6: Efficacy and safety results from phase III Einstein Extension

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto[a] 6 or 12 months N=602	Placebo 6 or 12 months N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)

Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

* $p < 0.0001$ (superiority), hazard ratio: 0.185 (0.087 - 0.393)

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Xarelto 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xarelto 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro*investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the

elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

Inter-ethnic differences

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - -4 h

and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E_{max}model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal 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.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate

Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 14, 28, 42 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

Bayer Pharma AG

13342 Berlin

Germany

8. Marketing authorisation number(s)

EU/1/08/472/011- 016

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30 September 2008

10. Date of revision of the text

05/2012

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

Distributed in the United Kingdom by:

Bayer plc

Bayer House

Strawberry Hill

Newbury

Berkshire

RG14 1JA

Appendix 1. UK SPC for rivaroxaban

Bayer plc

Bayer House, Strawberry Hill, Newbury, Berkshire, RG14 1JA

Telephone: +44 (0)1635 563 000

Fax: +44 (0)1635 563 393

WWW: http://www.bayer.co.uk

Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 18/06/2012

Xarelto 20mg film-coated tablets

1. Name of the medicinal product

Xarelto▼ 20 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 20 mg rivaroxaban.

Excipients with known effect:

Each 20 mg film-coated tablet contains 22.9 mg lactose monohydrate, see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet (tablet).

Brown-red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "20" and a triangle on the other side.

4. Clinical particulars

Appendix 1. UK SPC for rivaroxaban

4.1 Therapeutic indications

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.

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

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of DVT and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1-21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Xarelto immediately to ensure intake of 30 mg Xarelto per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Xarelto immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Appendix 1. UK SPC for rivaroxaban

Converting from Vitamin K Antagonists (VKA) to Xarelto

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is ≤ 3.0.

For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

Converting from Xarelto to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

Converting from parenteral anticoagulants to Xarelto

For patients currently receiving a parenteral anticoagulant, Xarelto should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Xarelto to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

Special populations

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

Elderly population

No dose adjustment (see section 5.2).

Body weight

No dose adjustment (see section 5.2).

Gender

No dose adjustment (see section 5.2).

Paediatric population

The safety and efficacy of Xarelto in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is not recommended for use in children below 18 years of age.

Method of administration

For oral use. The tablets are to be taken with food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast feeding (see section 4.6).

Appendix 1. UK SPC for rivaroxaban

4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

• congenital or acquired bleeding disorders

• uncontrolled severe arterial hypertension

• active ulcerative gastrointestinal disease

• recent gastrointestinal ulcerations

• vascular retinopathy

• recent intracranial or intracerebral haemorrhage

• intraspinal or intracerebral vascular abnormalities

• recent brain, spinal or ophthalmological surgery

• bronchiectasis or history of pulmonary bleeding.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.1 and 5.2).

Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Appendix 1. UK SPC for rivaroxaban

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant.

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. This increase is not considered clinically relevant.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

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

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

Appendix 1. UK SPC for rivaroxaban

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

4.6 Fertility, pregnancy and breast feeding

Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast feeding

Safety and efficacy of Xarelto have not been established in breast feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast feeding (see section 4.3). A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported to be common (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

Table 1: Number of patients studied, maximum daily dose and treatment duration in phase III studies

Indication	**Number of patients***	**Maximum daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately

1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

common (≥ 1/100 to < 1/10)

uncommon (≥ 1/1,000 to < 1/100)

rare (≥ 1/10,000 to < 1/1,000)

Not known: cannot be estimated from the available data.

Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery *(VTE-P),* treatment of DVT and prevention of recurrent DVT and PE *(DVT-T),* and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (*SPAF)*)

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
Tachycardia			
Vascular disorders			
Hypotension, haematoma			Pseudoaneurysm formation

			following percutaneous intervention*
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Haemoptysis		
Gastrointestinal disorders			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic function abnormal	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B])	Renal impairment (incl. blood creatinine increased, blood urea increased)[A]		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise), localised oedema[A]		
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	

Appendix 1. UK SPC for rivaroxaban

Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]			

A: observed in VTE-P after major orthopaedic surgery of the lower limbs

B: observed in DVT-T as very common in women < 55 years

*) These reactions ocurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

Appendix 1. UK SPC for rivaroxaban

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antithrombotic agents, ATC code: B01AX06

Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 16 to 33 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 s .

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests (see section 5.2).

Clinical efficacy and safety

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Appendix 1. UK SPC for rivaroxaban

Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 – 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 – 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 3.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 4).

Table 3: Efficacy results from phase III ROCKET AF

•	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value, test for superiority
Stroke and non-CNS systemic embolism	269 (2.12%)	306 (2.42%)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51%)	609 (4.81%)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and Myocardial infaction	659 (5.24%)	709 (5.65%)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99%)	281 (2.22%)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16%)	27 (0.21%)	0.74 (0.42 - 1.32) 0.308
Myocardial infaction	130 (1.02%)	142 (1.11%)	0.91 (0.72 - 1.16) 0.464

Table 4: Safety results from phase III ROCKET AF

Appendix 1. UK SPC for rivaroxaban

• Study population	• Patients with non-valvular atrial fibrillation[a]		
Treatment, dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment) Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value
Major and non-major clinically relevant bleeding events	1,475 (14.91%)	1,449 (14.52%)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60%)	386 (3.45%)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24%)	55 (0.48%)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82%)	133 (1.18%)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49%)	84 (0.74%)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305 (2.77%)	254 (2.26%)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65%)	149 (1.32%)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80%)	1,151 (11.37%)	1.04 (0.96 - 1.13) 0.345
All cause mortality	208 (1.87%)	250 (2.21%)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment

* Nominally significant

Treatment of DVT and prevention of recurrent DVT and PE

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall combined treatment duration in both studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical

judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (≥ 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p < 0.0001 (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 ((95% CI= 0.47–0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2 - 3) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI, 0.35 to 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

In the Einstein Extension study (see Table 6) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e.15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

Table 5: Efficacy and safety results from phase III Einstein DVT

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto[a] 3, 6 or 12 months N=1,731	Enoxaparin/VKA[b] 3, 6 or 12 months N=1,718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)

Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days followed by VKA

***** p < 0.0001 (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (superiority)

Table 6: Efficacy and safety results from phase III Einstein Extension

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto[a] 6 or 12 months N=602	Placebo 6 or 12 months N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

***** p < 0.0001 (superiority), hazard ratio: 0.185 (0.087 - 0.393)

Paediatric population

Appendix 1. UK SPC for rivaroxaban

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Xarelto 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xarelto 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Xarelto 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro*investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Appendix 1. UK SPC for rivaroxaban

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

Inter-ethnic differences

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E_{max}model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

Appendix 1. UK SPC for rivaroxaban

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal 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.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Microcrystalline cellulose

Croscarmellose sodium

Lactose monohydrate

Hypromellose

Sodium laurilsulfate

Magnesium stearate

Film-coat:

Macrogol 3350

Hypromellose

Titanium dioxide (E171)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 14, 28 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Appendix 1. UK SPC for rivaroxaban

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. Marketing authorisation holder

Bayer Pharma AG

13342 Berlin

Germany

8. Marketing authorisation number(s)

EU/1/08/472/017-021

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 30 September 2008

10. Date of revision of the text

05/2012

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

Distributed in the United Kingdom by:

Bayer plc

Bayer House

Strawberry Hill

Newbury

Berkshire

RG14 1JA

Appendix 2. Rare Adverse Events which are Serious and a high Proportion are due to drug

Agranulocytosis

Alveolitis

Anaemia aplastic

Anaphylaxis

Angioneurotic oedema

Arrhythmia

Bone marrow abnormal

Congenital abnormality

Dermatitis exfoliative

Disseminated intravascular coagulation

Erythema multiforme

Erythroderma

Guillain-Barre syndrome

Hepatic failure

Hepatitis

Jaundice

Leucopenia

Multiorgan failure

Nephritis

Nephrotic syndrome

Neuroleptic malignant syndrome

Neutropenia

Pancreatitis

Pancytopenia

Pseudomembranous colitis

Renal failure acute

Retroperitoneal fibrosis

Rhabdomyolysis

Stevens Johnson syndrome

Sudden Unexpected Death

Thrombocytopenia

Torsades de pointe

Toxic epidermal necrolysis

Any event for which there is a positive rechallenge