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

Protocol, Version 1.0

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TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

ADR	adverse drug reaction
AF	atrial fibrillation
BHC	Bayer HealthCare
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	confidence interval
DVT	deep vein thrombosis
EC	ethics committee
EDC	electronic data capture
EMA	European Medicines Agency
ENCePP	European Network of Centres of Pharmacoepidemiology and Pharmacovigilance
HCP	health care professional
HR	hazard ratio
INR	international normalised ratio
IRB	institutional review board
ITT	intention to treat
PE	pulmonary embolism
PVCH	BHC pharmacovigilance country head
RTI-HS	RTI Health Solutions
SPAF	stroke prevention in atrial fibrillation
TTR	time in target INR range of 2.0–3.0
UAT	user acceptance testing
UK	United Kingdom
US	United States

1 BACKGROUND

Xarelto© (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. It does not require routine coagulation monitoring and has no food interactions and only a few drug interactions compared to standard of care (Xarelto Summary of Product Characteristics—EU, 2011).

Rivaroxaban is currently indicated for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban has recently received a positive opinion by the European Committee for Medicinal Products for Human Use (CHMP) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) and treatment of deep vein thrombosis (DVT), and for prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults (Xarelto Summary of Product Characteristics—EU, 2011.)

Atrial fibrillation is the most common cardiac arrhythmia of clinical significance and is an important independent risk factor for cardiogenic thromboembolic events. The prevalence of AF increases with age, being less than 1% among people under 60 years of age, with estimates of more than 6% among those over 80 years of age (Feinberg et al., 1995). AF is estimated to affect over 6 million patients in Europe and approximately 2.3 million in the United States (US), and the number of patients with AF continues to grow in the ageing population (Kannel and Benjamin, 2008). AF is associated with a four- to five-fold increased risk of ischemic stroke (Wolf et al., 1991) and accounts for up to 15% of all strokes and 30% of strokes in patients over the age of 80 (Wolf et al., 1987). In addition, there is evidence that AF-associated stroke is more disabling than non–AF-associated stroke (Jorgensen et al., 1996).

Acute venous thromboembolism (i.e., DVT or PE) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1,000 persons in the general population and is the third most common cause of vascular death, after myocardial infarction and stroke. The current standard treatment for DVT is overlapping parenteral anticoagulation (i.e., low-molecular-weight heparin) and a vitamin K antagonist (i.e., warfarin). Parenteral anticoagulation needs to be continued for 5 to 7 days, at least until an international normalised ratio (INR) of 2.0 has been obtained, followed by a minimum of 3 months of treatment with the vitamin K antagonist. Treatment with vitamin K antagonists requires frequent monitoring of the INR, and multiple interactions of vitamin K antagonists with

foods and other drugs have been reported. The duration of treatment is determined by individual risk factors of the patient.

Two clinical programmes were undertaken to evaluate the efficacy and safety of rivaroxaban in the expanded indications.

- The ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for the Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was conducted to evaluate the efficacy and safety of rivaroxaban compared with the vitamin K antagonist warfarin in the prevention of thromboembolic events in patients with non-valvular AF. In the pivotal double-blind study, 14,264 patients were assigned to either Xarelto 20 mg once daily (15 mg once daily in patients with creatinine clearance 30-49 mL/min) or 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. Overall, 34.9% of patients were treated with acetylsalicylic acid, and 11.4% were treated with a class III antiarrhythmic, including amiodarone.

  Xarelto was non-inferior to warfarin for the primary composite endpoint of stroke and non–central nervous system systemic embolism (Kannel and Benjamin, 2008; Wolf et al., 1991). 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) (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.66–0.96; $P < 0.001$ for non-inferiority). Among all randomised patients analysed according to intention to treat (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). Among patients in the warfarin group, INR values were within the therapeutic range (2.0–3.0) a mean of 55% of the time (median, 58%; interquartile range, 43–71). 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.

- The EINSTEIN clinical trial programme was designed to evaluate the use of rivaroxaban for the acute treatment and secondary prevention of DVT (EINSTEIN-DVT) and PE (EINSTEIN-PE) and in long-term secondary prevention of recurrent DVT and PE (EINSTEIN-EXT). A unique aspect of the EINSTEIN-DVT and PE studies is the use of rivaroxaban as a single agent (single drug approach) in contrast to the use of intravenous anticoagulants and vitamin K antagonists.

  The EINSTEIN-DVT study demonstrated that rivaroxaban is at least as effective as

the current standard therapy, with similar safety, in the treatment and secondary prevention of DVT. EINSTEIN-EXT demonstrated that continued treatment with rivaroxaban 6 or 12 months after initial treatment is superior to placebo in preventing recurrences and has an acceptable risk of bleeding.

As a result of these programmes, Bayer HealthCare (BHC) pursued indications for the following:

- 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, aged ≥ 75 years, diabetes mellitus, and prior stroke or transient ischaemic attack.
- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults.

As a part of this safety risk management plan revision, a physician educational pack has been developed that includes the summary of product characteristics, prescriber guide (Appendix A), and patient card (Appendix B), with the aim to increase awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban.

The prescriber guide covers the following topics:

- Switching from or to rivaroxaban treatment
- Necessity of taking the 15-mg and 20-mg tablets with food
- Management of overdose situations
- Use of coagulation tests and their interpretation
- Dosing recommendations
- Perioperative management
- Populations at higher risk of bleeding
- Necessity of providing all patients with a patient card and counselling about the details of the patient card

The patient card contains the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a health care provider
- Importance of treatment compliance
- Necessity of taking the 15-mg and 20-mg tablets with food
- Necessity of carrying the patient card with them at all times

- Necessity of informing health care professionals (HCPs) that they are taking rivaroxaban if they need to have any surgery or invasive procedure

This protocol describes the planned evaluation of these elements of the risk management plan. Evaluations are planned for administration at 18 months, 3 years, and 7 years post-launch, and the status of these assessments will be presented regularly in periodic safety update reports.

2 SPECIFIC AIMS

The primary objective of this cross-sectional epidemiologic study is to measure physician and patient awareness and understanding of the key messages in the prescriber guide and patient card.

Specifically, the following objectives will be addressed:

- Investigate whether physicians and their patients have received the educational materials.
- Assess knowledge and understanding among physicians regarding key safety information contained in the prescriber guide and assess how physicians use the materials in their daily practice.
- Assess knowledge and understanding of patients regarding the key safety information contained in the patient card and determine if the patients use and carry the patient card with them.

3 STUDY DESIGN

3.1 Physician Assessment

3.1.1 Physician Assessment Overview

A geographically dispersed and diverse set of physicians prescribing rivaroxaban in the United Kingdom (UK), Germany, France, Italy, and Spain will be selected to reflect the distribution of physician specialities who prescribe rivaroxaban. Physicians will be asked to complete an online questionnaire evaluating their knowledge of key safety information as well as their receipt and use of the educational materials for rivaroxaban. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

3.1.2 Physician Population and Eligibility

This cross-sectional study will be conducted in each of the five countries (the UK, Germany, France, Italy, and Spain) with distribution among a variety of physician specialties including, for example, general practitioners, cardiologists (office and hospital), haematologists, hospital stroke physicians, emergency care physicians, phlebologists, neurologists, angiologists, and other specialists in internal medicine (office and hospital). Representation by each physician group will reflect, to the extent possible, prescribing patterns in each country. Physicians will complete an online questionnaire eliciting information about their knowledge and use of the prescriber guide for rivaroxaban.

Physicians will be eligible to participate in this study provided they have prescribed rivaroxaban to at least one patient in the past 6 months for one of the following indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF).
- Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults.

3.1.3 Physician Selection and Recruitment

The physician sampling frame will be constructed from either a physician panel or prescriber list. The final frame will be determined with the objective of achieving a generally representative sample of physicians prescribing rivaroxaban. Geographic location, speciality, practice size, practice type, etc. will be taken into consideration. If the distribution of physicians in the sampling frame appears consistent with the distribution believed in the targeted population, physicians will be randomly selected from the sample frame. However, if the distributions do not appear consistent with the targeted population, the sampling frame will be stratified by speciality and/or geography, and specific numbers of physicians within each stratum will be selected in order to recruit a sample that matches the distribution in the target population. In this case, the physician recruitment within each stratum will be done randomly. The final sampling strategy will be determined once rivaroxaban is on the market and will be designed to minimise bias and to allow for the study results to be generalised to the entire population of rivaroxaban prescribers to the extent feasible.

3.1.4 Physician Sample Size

The study will target 300 participating physicians per country, for a total of approximately 1,500 physicians overall, to allow reasonable precision around estimates of physicians' knowledge and understanding of the prescriber guide. For example, if we assume that the

total sample of participating physicians can be treated as a simple random sample and that the percent of correct responses to a true/false question is 85%, then for a sample of size 300, the two-sided 95% confidence interval will be 80.4% to 88.8%. Table 1 shows the exact 95% confidence limits assuming various combinations of sample size and correct response percentages.

Table 1. Exact 95% Confidence Limits for Various Combinations of Sample Size and Correct Response Percentage

Sample Size	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	80	70.8	87.3
100	85	76.5	91.4
300	80	75.0	84.4
300	85	80.4	88.8
500	80	76.2	83.4
500	85	81.6	88.0
1,500	80	77.9	82.0
1,500	85	83.1	86.8

3.1.5 Physician Questionnaire Development

Standard survey methodologic principles have been used to develop the physician questionnaire, which will assess physicians' knowledge of the following concepts as outlined in the prescriber guide and educational materials:

- Switching from or to rivaroxaban treatment
- Necessity of taking the 15-mg and 20-mg tablets with food
- Use of coagulation tests and their interpretation
- Dosing recommendations
- Perioperative management
- Populations at higher risk of bleeding
- Necessity of providing all patients with a patient card and counselling about the details of the patient card

Physicians will be asked about their receipt and use of the prescriber guide (Appendix A) as well as counselling of patients and distribution of the patient card. In addition, physicians will be asked to characterise their practice in terms of years in practice, size of practice, and

history of treating patients with the diagnoses of interest. Other characteristics will be collected to facilitate stratified analyses to explore factors associated with knowledge and behaviour. The physician questionnaire is designed to take 10-15 minutes to complete. A draft version of the questionnaire can be found in Appendix C. The physician questionnaire will be cognitively tested with physicians in each of the target countries. Section 3.3 provides a detailed description of the cognitive pretesting process. Modifications will be made to the questionnaire based on the pretesting results, and some variations to the questionnaire are anticipated based on country-specific requirements.

3.1.6 Physician Data Collection

A Web-based electronic data capture (EDC) system will be used in this study. An invitation will be sent to the selected sample of physicians, inviting them to participate and providing a link to the Web-based questionnaire. During the data collection period, invitations will be sent to each sampled physician up to two times. Each invited physician will be asked to log in to the study Web site by entering a unique identification number and password assigned to each participant and provided in the invitation to participate. The questionnaire will begin with informed consent. After participants consent, they will be prompted to complete the questionnaire. A screening question will be included at the beginning of the questionnaire to confirm that the physician has prescribed rivaroxaban at least once within the past 6 months for at least one of the two new indications.

The questionnaire will be self-administered (closed-ended questions with predefined answers) and can be completed at the participants' convenience. Although participants will be encouraged to complete the questionnaire in a timely manner, once they start the questionnaire, they will be able to stop at any point and, at a later time, pick up where they left off, should that be necessary. Participants will not be able to go back and change answers to previous questions. This restriction minimizes the likelihood of the respondent searching for answers via the web or other sources.

Participants will also not be allowed to access the questionnaire once it has been completed. Based on potential country specific requirements, the recruitment process and physician questionnaire may be different between countries. Country-specific differences will be described and appended to the final study protocol.

3.2 Patient Assessment

3.2.1 Patient Assessment Overview

Patients taking rivaroxaban will be identified through a diverse selection of medical practices representing specialties that prescribe rivaroxaban across the target countries. The medical practices selected for participation in the patient assessment will not be included in the physician assessment described above; however, they will be asked to complete the physician questionnaire to allow exploratory evaluation of the possible impact of the study on physician knowledge and to evaluate patient responses by level of knowledge of their physician. Patients will be invited to participate by their physicians and will complete a paper questionnaire. Data will be analysed using descriptive tables summarising demographics, results, and other available characteristics. Timing and sequence of study initiation in each country will be determined based upon the product launch schedule and timing of ethics approval.

3.2.2 Patient Population and Eligibility

Patients will be identified through selection of a diverse set of medical practices across the five targeted countries. To be eligible for the study, the patients must meet all of the following criteria:

- Patient has taken rivaroxaban within the last 3 months for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) or treatment of DVT and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
- Patient is aged 18 years or older.
- Patient is able to understand and complete the consent form and patient questionnaire.
- Patient can read and understand the native language of the country in which the study is being conducted.
- Patient has not participated in a clinical trial for a treatment to prevent blood clots in the past 12 months.

3.2.3 Patient Selection and Recruitment

The study will target a total of 500 patients (approximately 100 patients per country) to complete the assessment. This estimate is based upon the anticipated number of eligible patients for participation. This target study size is dependent upon the actual number of patients filling a prescription within the established time frame and on response rates for

the study. At least 10 physician practices in each country will be selected from a list of eligible physicians in order to identify and recruit a sufficient number of eligible patients (up to 10 patients per physician). Several factors will be evaluated to ensure a diverse representation of sites, including geographic location, physician specialty, and patient mix. To participate in the study, sites must (1) see a sufficient number of eligible patients; (2) be able to provide a semiprivate space for patient recruitment, the consent process, and completion of the patient-reported questionnaire; and (3) have a staff member available to coordinate research activities.

Physicians who are selected to participate in the patient assessment will be excluded from participating in the physician assessment.

Participating physicians will also be asked to collect a limited amount of de-identified information on all patients receiving rivaroxaban so that characteristics of participants can be compared with non-participants.

Patients will be eligible if they have taken rivaroxaban within the last 3 months for either SPAF or DVT treatment and secondary prevention. The patient sampling methodology will be designed with the goal of maximising the probability that each patient treated with rivaroxaban will have an equal opportunity to be selected. In some sites, it is likely that all treated patients will be selected. The sampling approach for those sites with larger numbers of patients will be customised for the site (based on patient volume) and will be devised to achieve an efficient method of obtaining a representative patient sample in centres with varying patient administration systems. The sites will be asked to recruit the patients for the study when the patient is at the physician practice for a previously scheduled visit, or by telephone.

3.2.4 Patient Sample Size

The study will target 100 patients per country, for a total 500 patients overall, to allow reasonable precision around estimates of patients' knowledge and understanding of the patient card at the study level. Since we plan to recruit up to 10 patients per physician practice, the responses from patients within the same practice may be correlated. Assuming no intraclass correlation and the percentage of correct responses to a true/false question is 50.0%, then for a sample of size 500, the two-sided 95% confidence interval will be 45.6% to 54.4%; whereas the corresponding confidence interval will be 41.2% to 58.8% if there is an intraclass correlation of 0.33. Table 2 shows 95% confidence limits assuming various combinations of sample size, correct response percentages, and intra-class correlation coefficients.

Table 2. Confidence Limits (95%) for Various Combinations of Sample Size, Correct Response Percentage, and Intraclass Correlation Coefficient

Patient Sample Size	Intraclass Correlation Coefficient[a]	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
100	0.00	50	40.2	59.8
100	0.11	50	36.1	63.9
100	0.33	50	30.4	69.6
100	0.00	80	72.2	87.8
100	0.11	80	68.9	91.1
100	0.33	80	64.3	95.7
200	0.00	50	43.1	56.9
200	0.11	50	40.2	59.8
200	0.33	50	36.1	63.9
200	0.00	80	74.5	85.5
200	0.11	80	72.2	87.8
200	0.33	80	68.9	91.1
500	0.00	50	45.6	54.4
500	0.11	50	43.8	56.2
500	0.33	50	41.2	58.8
500	0.00	80	76.5	83.5
500	0.11	80	75.0	85.0
500	0.33	80	73.0	87.0

Note: Table calculations assume that, on average, 10 patients come from each practice (cluster).

[a] With an average cluster size of 10 patients, correlation coefficients of 0.11 and 0.33 correspond with a design effect of 2 and 4, respectively.

3.2.5 Patient Questionnaire Development

The patient questionnaire has also been developed following standard survey methodologic principles and will be cognitively tested with patients in each of the target countries. Modifications will be made to the questionnaire based on the results of testing, and some variations to the questionnaire are anticipated based on country-specific requirements. The questionnaire will assess patient knowledge of the following concepts (please refer to Appendix D for the draft questionnaire):

- Receipt and use of the patient card

- Knowledge of the key safety messages outlined in the patient card:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider
  - Importance of treatment compliance
  - Necessity of taking the 15-mg and 20-mg tablets with food
  - Necessity of carrying the patient card at all times
  - Necessity of informing HCPs that they are taking rivaroxaban if they need to have surgery or invasive procedures

The questionnaire includes demographics and other patient information to help characterise patterns of knowledge and behaviour through stratification of results. The questionnaire has been designed to take no more than 15 minutes to complete.

3.2.6 Patient Data Collection

The patient questionnaire will be self-administered (closed-ended questions with predefined answers) on a hard copy form at the site. While there are a number of advantages to using an electronic format for questionnaire administration, we anticipate a paper format will be preferred in this case based on the study population (e.g., older patients). Written informed consent will be obtained from each patient prior to completion of this questionnaire.

Patients will be asked to complete the questionnaire in the physician's office in a private setting. Sites will provide patients with appropriate privacy so there is no influence by the physician (or patient perception thereof) in this process. Patients will place their completed questionnaires in an envelope and give the sealed envelope to a study coordinator or designee. While participating physicians will be informed of the purpose of the study, they will be counselled not to alter routine practice and patient education so as not to influence the study results. Physicians will be advised that the ultimate goal of the study is to evaluate the educational materials.

3.3 Cognitive Pretesting

In order to thoroughly evaluate the physician and patient questionnaires before fielding the study, RTI Health Solutions (RTI-HS) will conduct cognitive pretesting with physicians and patients in each country.

Cognitive pretest interviewing is a well-established qualitative research methodology used to identify problems with questionnaire items and response options (Groves et al., 2009). Specifically, trained interviewers will ask pretest participants to complete the questionnaires while thinking aloud or describing their thought processes as they answer the questionnaire

items. Pretest interviewers will use an interview guide that includes probe questions designed to help interviewers understand how each participant interpreted and chose his or her answers for each item in the draft questionnaires. The pretest interviews will be designed to help identify problems with questionnaire items, wording, response choices, etc., and ensure that participants understand the questions. The pretest interview data will be used to optimise the language used in the questionnaires prior to fielding the patient and physician assessments. Likewise, the cognitive testing will help identify cultural or translational issues with the draft questionnaires so that they can be modified to meet the individual needs of each country while maintaining comparability across the study.

The pretest interviews also will provide an opportunity to test procedures and introductory materials in an effort to increase participation and thoughtful consideration of the questionnaires by participants during collection of the study data.

Cognitive pretesting of the physician questionnaire will be conducted with up to five physicians in each of the five countries who prescribe rivaroxaban for SPAF or DVT treatment and secondary prevention. Additionally, cognitive pretesting of the patient questionnaire will also be conducted with four to six patients in each country who are currently being treated for SPAF or DVT/PE.

3.4 Adverse Event Reporting

This study is not designed to collect information on individual adverse drug events, which are better collected using other study designs. However, spontaneous adverse drug reactions (ADRs) may be identified through the following pathways:

- Communicated during the qualitative cognitive pretesting interviews
- Documented through open-ended responses (if applicable) in the Web questionnaire completed by the HCP
- Documented through open-ended questions (if applicable) or handwritten notes on the questionnaire completed by the patient

For the cognitive pretest interviews, the interviewer will be undergo safety training and will complete an ADR case report form if a spontaneous ADR is reported. The case report form will be submitted to the BHC pharmacovigilance country head (PVCH).

For each assessment, questionnaire data will be reviewed for possible ADRs. Upon identification of an ADR, this information will be forwarded to the BHC PVCH within 1 business day by e-mail, fax, or other mechanism developed with BHC. BHC will assess the information for possible adverse events and product complaints and forward it for processing to the company safety database and/or to the Product Complaints group as applicable through BHC's usual reporting processes and standard operating procedures. The

local contact to the PVCH will follow up with the adverse event, if BHC determines that follow-up is needed and if the reporting patient has given consent to be contacted by BHC. All initial and follow-up information will be de-identified and reported to BHC.

If a patient spontaneously reports an ADR to a physician during their participation in the study at the site, physicians will be expected to report suspected ADRs to the applicable manufacturer/licensee and/or regulatory authority in accordance with local procedures.

3.5 Ethical and Scientific Aspects

3.5.1 Protection of Human Subjects

This study will be conducted in accordance with all applicable ethical and regulatory requirements, including, where applicable, the 1996 version of the Declaration of Helsinki. The institutional review board (IRB) at RTI International (of which RTI-HS is a division) will review the study protocol, questionnaires, and informed consent documents. IRB/ethics committee (EC) approvals will be obtained in accordance with applicable national and local regulations in each country.

3.5.2 Ethical, Regulatory, and Scientific Principles

This study is being conducted as a regulatory commitment. As an observational study, the risks for patients linked to their participation in the study are limited to a breach of confidentiality with regard to personal identifiers or health information. Before a patient can participate in the study, he or she must give informed consent. Independent EC approval will be according to the guidance of the each country's research ethics requirements.

The study will be conducted under the following guidelines:

- The International Society for Pharmacoepidemiology 2008 *Guidelines for Good Pharmacoepidemiology Practices (GPP)* (http://www.pharmacoepi.org/resources/guidelines_08027.cfm)
- The Council for International Organizations of Medical Sciences (CIOMS) 2009 *International Ethical Guidelines for Epidemiological Studies* (http://www.cioms.ch/frame_ethical_guidelines_2009.htm)
- CIOMS 2002 *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (www.fhi.org/training/fr/retc/pdf_files/cioms.pdf)

- The study will be designed in line with the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) (2011) *Guide on Methodological Standards in Pharmacoepidemiology* (http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf)
- The study will reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist (http://www.strobe-statement.org/index.php?id=available-checklists).
- The study will comply with the definition of a non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of *Volume 9A of the Rules Governing Medicinal Products in the European Union* (http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm).

3.5.3 Informed Consent

Participant informed consent will be obtained for each patient or physician who agrees to complete a questionnaire. Patient informed consent will be obtained in writing in all participating countries. Physicians will be asked to provide electronic acknowledgement of consent prior to completing the Web-based questionnaire.

The questionnaires will not collect any identifying information about the patient or physician, and they will be tracked using a unique study identifying number. For paper questionnaires, the physician will record the patient's study number on the questionnaire before it is given to the patient. Physicians will be required to provide limited data on each participating patient (e.g., diagnosis, surgeries, and treatment duration).

3.5.4 Participant Confidentiality

The research team will not have access to any participant-identifying information. No personal identifying information will be removed from the centres. Only de-identified data will be made available to the research staff and BHC. Thus, any reports that are generated will *not* contain any participant identifiers. Data will be provided to BHC in aggregate only and will not be linked to individual patients or HCPs.

For the patient assessment, sites will maintain an enrolment log with only the names of patients who completed the study and HCPs involved in the study. Site logs will be maintained at the site and will never be shared with the research team, third parties, or BHC. Additionally, the patient questionnaire will *not* be linked to any patient log or any other patient-identifying information. Additionally, age in lieu of a birth date will be used to further protect confidentiality.

3.5.5 Compensation

Physician sites participating in the patient assessment will be paid nominal incentives to compensate them for the time spent recruiting patients and providing limited data from patient records, per country-specific regulations. The amount and payment methods will be reviewed and approved by the IRB/EC to ensure that payments are commensurate with the time needed to complete the study tasks and are not coercive.

Patients and physicians participating in the assessments will be paid nominal incentives to compensate them for their time in completing the study questionnaires in those countries where it is acceptable to do so. As with the site compensation, the amount and payment methods will be reviewed and approved by the IRB/EC to ensure that payments are commensurate with the time needed to complete the forms, not coercive, and made according to local regulations in each country.

3.6 Data Management

A data management plan will be developed to guide the handling of data, including the transfer of electronic files. The data management plan will include, if necessary, country-specific modifications due to local regulations or requirements. Physician data will be entered directly into a Web-based EDC system. Patients will fill out data on paper forms, which will be sent to a data processing centre for double data entry that will be used to minimise data entry errors. Edit and logic checks will be conducted and queries resolved to ensure high-quality data. However, due to the self-reported nature of the data some such resolutions may not be possible.

RTI-HS data managers will conduct user acceptance testing (UAT) and will sign the UAT report before the EDC system is used in the field. Staff will be trained on data collection forms and the EDC system before the study is fielded. RTI-HS data managers will approve the data management plan, all annotated data collection forms, the EDC and double–data entry system data dictionaries, the data cleaning specifications document, and the testing summary reports before authorizing the data systems to go "live." RTI-HS data managers will ensure that the EDC and paper data systems are tested and valid, and will require that testing documentation, database documentation, and change control documentation will be created and maintained.

Once the systems are is in the field, data management activities will include review of interim analysis files for consistency, programming edit checks in preparation for statistical analysis, and merging datasets if required.

3.6.1 Quality Assurance and Quality Control

This project will be conducted in accordance with the above guidances and the internal standard operating procedures of participating institutions. The RTI Health Solutions (RTI-HS) Office of Quality Assurance, an independent unit that reports to the Vice President of RTI-HS, will oversee quality assurance for this study.

3.6.2 Record Retention

A copy of all the study materials (informed consent forms, patient questionnaires) will be retained according to Bayer's standard operating procedures and in keeping with local regulatory requirements.

Any paper data files collected in the European Union will be maintained within the European Union. Only data based on case identification numbers will be transferred to the US for the purpose of analysis and generation of the final report. Data analysis and storage of de-identified data sets will be in the US.

4 ANALYSIS AND INTERPRETATION

Analyses will include detailed review of responses to individual questions as well as potential summary measure across logical grouping of response items. Physician results will be stratified by country, speciality, and other logical variables. Patient results will be stratified by country and other logical variables, potentially including a measure of the knowledge level of their physician. A detailed analysis plan describing methods of analysis and presentation, as well as table shells, will be developed prior to starting analysis of data. In addition to a description of the analysis of the questionnaire data, the analysis plan will describe any planned comparisons of participants and non-participants; this will depend upon data available on non-participants.

The analysis plan will also describe the following:

- Analysis of subgroups
- Methods for handling missing data
- Level of statistical precision

All analyses will be performed using SAS 9.2 (or higher) statistical software (SAS, Cary, North Carolina). Programmes, logs, and output will be reviewed for accuracy according to relevant standard operating procedures.

Descriptive tables summarising demographics, results, and other available characteristics will be generated for the physicians and patients by country. For continuous-type data, the

mean, standard deviation, median, and range will be presented. For categorical data, frequencies and percents will be reported. The specific tables to be included will be finalised in the analysis plan.

Whenever possible, we will provide comparisons of participants to non-participants, and/or compare characteristics of the participants to what is known about the overall physician and patient populations. In addition, exploratory analyses will be conducted comparing responses between the physicians who participated in only the physician questionnaire component of the study to those who also recruited patients into the patient component to explore the potential that the study itself created greater awareness of the safety information. Multivariable analyses may be conducted to evaluate predictors of high/low knowledge levels.

5 STRENGTHS AND LIMITATIONS

A key strength of the study is the diversity of the sites, physicians, and patient populations to be included in both assessments. Based on available information, geographic location, and physician practice type (clinic, hospital, internists, haematologists, etc.), sites and patients recruited for participation will constitute a generally representative sample of rivaroxaban prescribers and users. However, given the potential delay in product uptake, it might be challenging to ensure that the finally selected centres, prescribers, and patients are fully representative of the existing patient population across countries and different types of centres. Critical to the goal of capturing detailed patient information will be identification of physicians and patients who have been introduced to rivaroxaban and the newly approved indications.

The physician assessment will be conducted after physicians have received the prescriber guide and have had a chance to utilise that guide in their practice. This portion of the study will evaluate how physicians are using the materials in their daily practice with patients.

The patient questionnaire will be conducted after patients have received rivaroxaban. Therefore, the study will evaluate recall about the process of receiving and reading the patient card, awareness of the key information contained in the patient card, and whether the patient carries the patient card during treatment.

Among the strengths of the patient assessment will be the collection of information on participants and on non-participants. Sites will keep a simple log with information on the number of patients approached about the study, the number of patients confirmed eligible, and the number of patients who refused. Site logs will be produced weekly during the data collection period. These data will allow calculation of the participation rate. Patients who are approached by the study coordinator and then refuse to participate will be asked the reason

for refusal. Reasons for non-participation will be described in the report. In addition, we will compare characteristics of the participants with those of the total rivaroxaban patients to evaluate any differences that should be considered in the analysis.

Other strengths of the patient assessment include the probability of high response rates given that the study is being introduced to patients by a trusted HCP, and the ability to stratify knowledge results based on duration of use, patient use and receipt of the patient card, and provider knowledge.

The study will target a total of 1,500 physicians (approximately 300 per country) and 500 patients (approximately 100 patients per country) to complete the assessment. The majority of the analysis will focus on aggregated data. Although the report may display country-specific findings, there may be limitations with drawing country-specific conclusions, particularly for the patient assessment given the relatively small samples sizes within each country.

As with all voluntary studies, some limitations are inherent. Although the study is designed to ensure the selection of a diverse and generally representative sample of prescribers and patients to participate in this study, there exists no exhaustive list of all rivaroxaban prescribers and patients from which to draw a sample; hence, it is impossible to select a random sample of all prescribers/patients. Therefore, the study participants may not necessarily represent all users of rivaroxaban. In addition, as is true with most surveys, it is possible that respondents who complete the questionnaire will differ from non-respondents in characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials). The direction and magnitude of such potential respondent bias is not known. In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., Internet access). However, it is anticipated that the majority of physicians will be Internet enabled.

Another potential limitation of the patient assessment is that the study could influence sites to provide more education to patients than they normally would provide. To minimize this risk, sites will be trained to provide only limited information about the study prior to the patients' participation in the study, and patients will be asked to complete the questionnaire at the site prior to receiving any additional counseling about treatment. In addition, it is not possible to restrict patients from changing their responses on the paper questionnaire based on information learned as they complete the questionnaire. However, the questionnaire will emphasize that the patients should respond based on what they know and explain that the ultimate goal of the study is to make sure that patients are well informed about their medications.

6 ROLES AND RESPONSIBILITIES

- RTI-HS, an independent non-profit research organisation has developed this protocol and has responsibility for the design, conduct, analysis, and reporting of the study.
- BHC is the sponsor of the study. Scientists from BHC will collaborate in the design.
  - BHC will be responsible for fulfilling any responsibilities for reporting results to regulatory agencies.
- Kantar Health will be responsible for physician recruitment for the physician and patient assessments, monitoring sites for patient recruitment, data collection, cognitive pretesting, and ethics submissions.

7 COMMUNICATION

The protocol, study status updates, and report(s) will be included in regulatory communications in line with the risk minimisation plan, periodic safety update reports, and other regulatory milestones and requirements.

In the case of communications in other settings (such as conferences or publications), abstracts, presentations, and manuscripts will be prepared in accordance with the guidelines of the International Society for Pharmacoepidemiology (2008) and the International Committee of Medical Journal Editors (2010).

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Appendix A.
Xarelto Prescriber Guide

(Submitted with the EU-RMP)

Xarelto® rivaroxaban Prescriber Guide

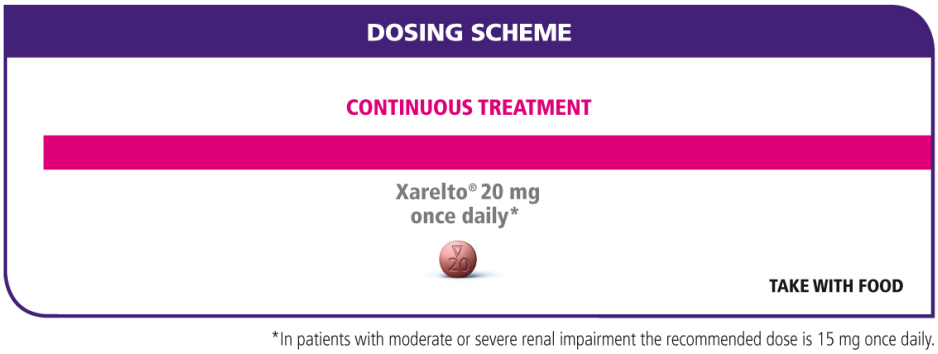
PATIENT ALERT CARD

A patient alert card must be provided to each patient who is prescribed Xarelto® 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance and signs of bleeding and when to seek medical attention should be discussed with the patient.
The patient alert card will inform physicians and dentists about the patient‘s anticoagulation treatment and will contain emergency contact information.
The patient should be instructed to carry the patient alert card at all times and present it to every health care provider.

DOSING RECOMMENDATIONS

Dosing in patients with atrial fibrillation

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation is 20 mg once daily.

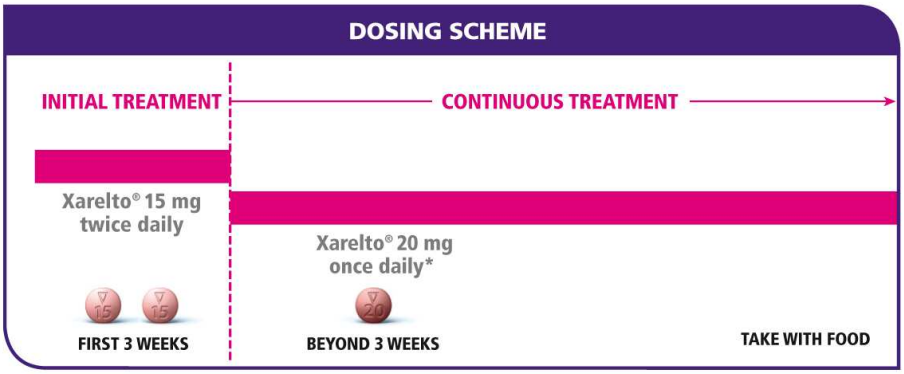


Patients with renal impairment:
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment the recommended dose is 15 mg once daily.
Use is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:
Xarelto® should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding.

Missed dose:
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.

Dosing in the treatment of deep vein thrombosis (DVT) and secondary prevention of DVT and pulmonary embolism (PE)
Patients are initially treated with 15 mg **twice daily** for the first three weeks.
This initial treatment is followed by 20 mg **once daily** for continued treatment period.



*In patients with moderate or severe renal impairment the recommended dose is 15 mg once daily.

Patients with renal impairment:
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily.
Use is not recommended in patients with creatinine clearance < 15 ml/min.

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

Missed dose:
- **Twice-daily treatment period** (15 mg bid for the first three weeks): If a dose is missed, the patient should take Xarelto® immediately to ensure intake of 30 mg Xarelto® per day. Continue with the regular 15 mg twice daily intake on the following day.
- **Once-daily treatment period** (beyond three weeks): 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.

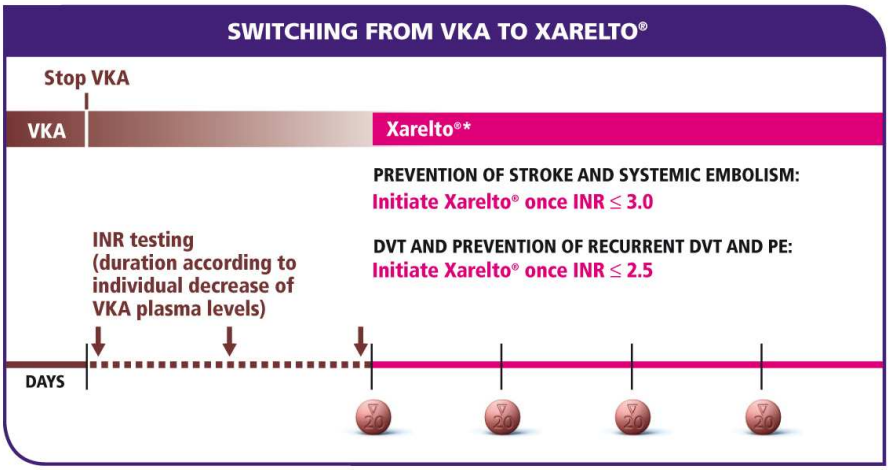
ORAL INTAKE
Xarelto® 15 mg and 20 mg must be taken with food. The intake of these doses with food at the same time support the required absorption of the drug, thus ensuring a high oral bioavailability.
Note: Xarelto® is also available at a 10 mg dose for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. This dose can be taken without food.

PERIOPERATIVE MANAGEMENT
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.

CONVERTING FROM VKA TO XARELTO®

For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA 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**, treatment with VKA should be stopped and Xarelto® therapy should be initiated when the **INR** is **≤ 2.5**.



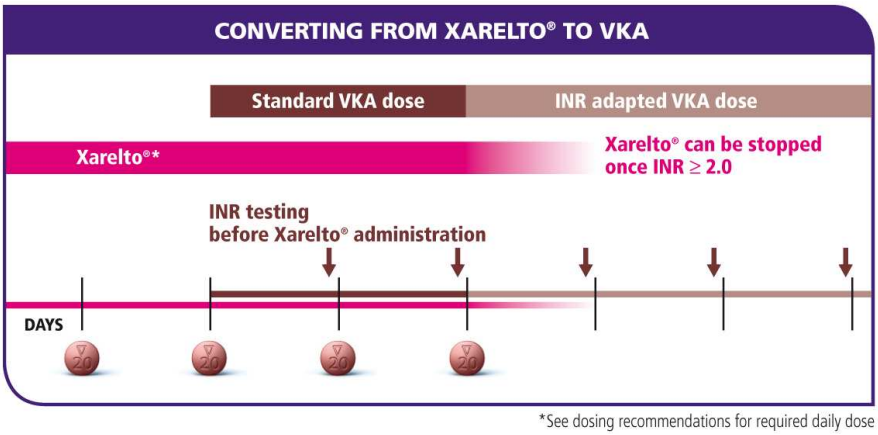
*See dosing recommendations for required daily dose

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto®, and therefore should not be used for this purpose. Treatment with Xarelto® only does not require routine coagulation monitoring.

CONVERTING FROM XARELTO® TO VKA

It is important to ensure adequate anticoagulation while minimizing the risk of bleeding during conversion of therapy.

When converting to VKA, Xarelto® and VKA should be given overlapping 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.



*See dosing recommendations for required daily dose

INR measurement is not appropriate to measure the anticoagulant activity of Xarelto®. 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.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO XARELTO®

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Xarelto® should be started at the time of discontinuation.

- Patients with parenteral drug on a fixed dosing scheme such as LMWH: Xarelto® should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM XARELTO® TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given instead of the next Xarelto® dose at the same time.

POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

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

Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications:

- *Patients with renal impairment:* See "dosing recommendations" for patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment. Xarelto® use is not recommended in patients with creatinine clearance <15 ml/min
- *Patients with 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
- *Patients concomitantly receiving other medicinal products*
  - Systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): **use of Xarelto® is not recommended**
  - Drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents
- *Patients with other haemorragic risk factors such as*
  - 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

Xarelto® is contraindicated during pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto®.

OVERDOSE
Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg Xarelto® and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.
Should a bleeding complication arise in a patient receiving Xarelto®, the next Xarelto® administration should be delayed or treatment should be discontinued as appropriate.

Individualized bleeding management may include

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Haemodynamic support; blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with 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 Xarelto®.

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

COAGULATION TESTING
Xarelto® does not require routine coagulation monitoring.
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated international normalized ratio (INR).
Especially INR testing was developed for measuring VKA-effects and is therefore not appropriate to measure activity of Xarelto®. Dosing- or treatment decisions should not be based on results of INR except when converting from Xarelto® to VKA as described above.

If clinically indicated haemostatic status can be assessed by PT using Neoplastin as described in the SmPC.

Appendix B.
Xarelto Patient Card

(Submitted with the EU-RMP)

What should I know about Xarelto®?

- Xarelto® thins the blood, which prevents you from dangerous blood clots.
- Xarelto® must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, never skip a dose.
- You must not stop taking Xarelto® without first talking to your doctor as your risk of blood clots may increase.
- Speak to your health care provider prior to any intake of other medication.
- Inform your health care providers about Xarelto® intake prior to any surgery or invasive procedure.

Bayer HealthCare

When should I seek advice from my health care provider?

When taking a blood thinner such as Xarelto® it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Xarelto® if you are at risk of abnormal bleeding, without first discussing this with your doctor.

Tell your health care provider right away if you have any signs or symptoms of bleeding such as the following:

- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, bleeding from cuts that take a long time to stop
- menstrual flow or vaginal bleeding that is heavier than normal
- pink or brown urine, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds

How do I take Xarelto®?

- To ensure optimal protection, Xarelto® 15 mg and 20 mg must be taken with food.

Xarelto® rivaroxaban

Patient Card

Xarelto® 15 mg
Xarelto® 20 mg

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

I am under anticoagulation treatment with Xarelto® (rivaroxaban).

Name

Address

Birth date

Weight

Blood type

Other medications / conditions

In case of emergency, please notify:

Doctor's name

Doctor's phone

Doctor's stamp:

Please also notify:

Name

Phone

Relationship

Information for health care providers:

- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto®.

Appendix C.
Physician Questionnaire

Xarelto Risk Minimisation Evaluation – Physician Questionnaire

Study Objective

RTI International, an independent, nonprofit research firm engaging in numerous health and medicine research studies, is conducting a research study on behalf of Bayer Health Care (BHC) and would like to invite you to participate. This study is being conducted as part of the ongoing safety and risk management process for Xarelto (rivaroxaban). The purpose of the study is to assess prescribers' understanding of and compliance with the safe use of Xarelto (rivaroxaban) for the following two chronic indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF)
- Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. (This indication will be referred to as DVT treatment and secondary prevention throughout the questionnaire.)

You have been identified as a potential participant for this evaluation because you are a physician who treats patients who have, or who are at risk for developing these conditions. This questionnaire is being administered to approximately 1,500 physicians across several countries within the European Union (EU). To confirm your eligibility to participate in this brief (approximately 10 to 15 minute) assessment, please answer the following question:

S1. In the past 6 months, have you prescribed Xarelto (rivaroxaban) to patients for either of the following new indications?

(Check all that apply.)

- ☐ Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF)
- ☐ Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults
- ☐ I have not prescribed Xarelto (rivaroxaban) for either of these indications [TERMINATE]

[PROGRAMMING NOTE: IF TERMINATED, DISPLAY MESSAGE, "We are only including physicians who have prescribed Xarelto (rivaroxaban) in the past 6 months for one of these two indications. Thank you for your time."]

[PROGRAMMING NOTE: IF ELIGIBLE: "Thank you for answering this question. You are eligible to participate in this study."]

What Will Happen

As a part of this study, you will be asked to complete a questionnaire related to your general knowledge about Xarelto (rivaroxaban). The questionnaire will take approximately 10 to 15 minutes to complete. As compensation for your time, you will receive €XX for your participation in the study and completion of the questionnaire.

Confidentiality

Any information you provide to us is confidential, and every precaution will be taken to protect your privacy. Your responses will be used only for statistical purposes and will not be disclosed or used in any personally identifiable form for any other purpose, unless otherwise compelled by law. Your answers will be kept strictly confidential and will not be linked to your name in any report or publication. The risk of participation in this study relates to data security and is minimal, given the strict confidentiality and security procedures in place.

There are no direct benefits to you from participating in this study. Your willingness to take part in this study will help us ensure that the key safety messages about Xarelto (rivaroxaban) are being effectively communicated to you and your patients.

If you have any questions about the study, you can call project staff, at (EU toll-free number).

Informed Consent

Please indicate below that you have read the study information provided above.

- ☐ Yes, I have read the information provided above. The study purpose and procedures are clear to me.
- ☐ No. [PROGRAMMING NOTE: Only prescribers who agree to consent can participate in the study.]

Please indicate below if you agree to participate in the current study.

- ☐ Yes, I agree to participate in this study.
- ☐ No, I do not agree to participate in this study. [PROGRAMMING NOTE: Only prescribers who agree to consent can participate in the study.]

Physician Questionnaire

Although, Xarelto (rivaroxaban) is approved for the prevention of DVT and potential PE in patients undergoing elective knee or hip surgery, this questionnaire is designed to gain a better understanding of prescribers' knowledge about the prescribing and administration of Xarelto (rivaroxaban) (Xarelto tablets) to patients for only the following two indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF)

- Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults. (This indication will be referred to as DVT treatment and secondary prevention throughout the questionnaire.)

Additionally, this assessment will be used to determine if the education materials regarding Xarelto (rivaroxaban), including the Prescriber Guide, are understood properly and whether there are aspects of these materials that could be improved.

Physician Questionnaire

The following questions ask about the use of Xarelto (rivaroxaban) for SPAF and DVT treatment and secondary prevention.

Note: An asterisk (*) indicates correct responses for review purposes

Q1. What is the most important risk associated with taking Xarelto (rivaroxaban)?

(Check one.)

- ☐ Osteosarcoma
- ☐ Increased blood pressure
- ☐ Increased risk of bleeding*
- ☐ Suppressed immunity
- ☐ I don't know

Q2. Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto (rivaroxaban)?

(Check Yes, No, or I don't know for each patient population listed)

Population	**Yes,** at higher risk	**No**, not at higher risk	**I don't know**
Patients with moderate or severe renal impairment	☐ Yes*	☐ No	☐ I don't know
Patients taking vitamin D	☐ Yes	☐ No*	☐ I don't know
Patients taking systemic azole-antimycotics or HIV protease inhibitors	☐ Yes*	☐ No	☐ I don't know
Patients taking products that affect haemostasis	☐ Yes*	☐ No	☐ I don't know
Patients with haemorrhagic risk factors (e.g., uncontrolled severe arterial hypertension, gastrointestinal ulceration)	☐ Yes*	☐ No	☐ I don't know
Patients with chronic constipation	☐ Yes	☐ No*	☐ I don't know

Q3. To which of the following patient groups is it appropriate to prescribe Xarelto (rivaroxaban)?

(Check all that apply.)

- ☐ Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- ☐ Patients who are pregnant
- ☐ Patients with creatinine clearance < 15 mL/min
- ☐ None of the above*
- ☐ I don't know

Q4. Xarelto (rivaroxaban) 15 mg and 20 mg must be taken…. ?

(Check one.)

- ☐ On an empty stomach
- ☐ With food*
- ☐ 1 hour before eating
- ☐ None of the above
- ☐ I don't know

Q5. Is routine coagulation monitoring required for patients taking Xarelto (rivaroxaban) for these indications?

- ☐ Yes
- ☐ No*
- ☐ I don't know

Q6. The international normalised ratio (INR) is appropriate to measure the anticoagulant activity of Xarelto (rivaroxaban).

- ☐ Yes, INR is appropriate to measure the anticoagulant activity of Xarelto (rivaroxaban)
- ☐ No, INR is only appropriate to measure the anticoagulant activity of vitamin K antagonists*
- ☐ I don't know

Q7. In which of the following situations should INR be tested in current or potential Xarelto (rivaroxaban) users?

(Check all that apply.)

- ☐ When switching from vitamin K antagonist (VKA) to Xarelto (rivaroxaban)*
- ☐ When switching from Xarelto (rivaroxaban) to a VKA*
- ☐ Continual INR monitoring is required for all patients taking Xarelto (rivaroxaban)
- ☐ I don't know

Q8. When converting from parenteral anticoagulants to Xarelto (rivaroxaban)…?

(Check all that apply.)

- ☐ Patients should stop taking parenteral anticoagulants for a week prior to starting Xarelto (rivaroxaban)
- ☐ For patients with continuously administered parenteral drug, Xarelto (rivaroxaban) should be started at time of drug discontinuation*
- ☐ For patients on a fixed dosing scheme, Xarelto (rivaroxaban) should be started 0 to 2 hours before the time of the next scheduled drug administration*
- ☐ Xarelto (rivaroxaban) is not recommended in patients who have taken parenteral anticoagulants
- ☐ I don't know

Q9. What are the key steps to ensure adequate anticoagulation while minimising the risk of bleeding when converting patients from Xarelto (rivaroxaban) to VKA?

(Check all that apply.)

- ☐ Overlapping of the two drugs should occur until INR is $\geq$ 2.0*
- ☐ While overlapping both drugs, INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto (rivaroxaban)*
- ☐ Xarelto (rivaroxaban) can be stopped at anytime
- ☐ INR can be measured at any time of the day
- ☐ I don't know

Q10. What are the key steps to ensure adequate anticoagulation while minimising the risk of bleeding when converting patients from VKA to Xarelto (rivaroxaban)?

(Check all that apply.)

- ☐ Stop VKA without measuring INR
- ☐ For patients treated for SPAF, treatment with VKA should be stopped and Xarelto (rivaroxaban) initiated when INR is $\leq$ 3*
- ☐ For patients treated for DVT treatment and secondary prevention, treatment with VKA should be stopped and Xarelto (rivaroxaban) initiated when INR is $\leq$ 2.5*
- ☐ I don't know

Q11. Which of the following is the most appropriate timing for measuring INR when converting to or from Xarelto (rivaroxaban)?

(Check one.)

- ☐ Immediately after intake of Xarelto (rivaroxaban)
- ☐ 2 hours after intake of Xarelto (rivaroxaban)
- ☐ Not earlier than 24 hours after the previous dose but prior to the next dose of Xarelto (rivaroxaban)*
- ☐ I don't know

Q12. If an invasive procedure or surgical intervention is required, Xarelto (rivaroxaban) should be stopped…?

(Check one.)

- ☐ One week prior to the procedure or surgical intervention if possible, based upon clinical judgment of the physician
- ☐ 12 hours prior to the procedure or surgical intervention if possible, based upon clinical judgment of the physician
- ☐ At least 24 hours prior to the procedure or surgical intervention if possible, based upon clinical judgment of the physician*
- ☐ It is not recommended that Xarelto (rivaroxaban) be stopped for these procedures
- ☐ I don't know

Q13. What are the most appropriate actions you should take if a patient presents with a bleeding complication?

(Check all that apply.)

- ☐ Provide symptomatic treatment (e.g., mechanical compression, surgery)*
- ☐ Delay the next administration of Xarelto (rivaroxaban) or discontinue Xarelto (rivaroxaban) as appropriate*
- ☐ Provide haemodynamic support (e.g., blood transfusion)*
- ☐ Administer procoagulant reversal agent (for life-threatening bleeding)*
- ☐ None of the above
- ☐ I don't know

The following questions are about the indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (the SPAF indication). If you have not prescribed Xarelto (rivaroxaban) for SPAF, please check the response indicating that you do not prescribe for this indication.

Q14. What is the standard recommended dose of Xarelto (rivaroxaban) for prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation?

(Check one.)

- ☐ 20 mg taken once a day*
- ☐ 15 mg taken once a day
- ☐ 10 mg taken twice a day
- ☐ None of the above
- ☐ I do not prescribe for this indication
- ☐ I don't know

Q15. What is the recommended dose for patients with moderate or severe renal impairment (creatinine clearance of 15-49 mL/min) receiving Xarelto (rivaroxaban) for a SPAF indication?

(Check one.)

- ☐ 20 mg taken once a day
- ☐ 15 mg taken once a day*
- ☐ 10 mg taken twice a day
- ☐ None of the above
- ☐ I do not prescribe for this indication
- ☐ I don't know

The following questions are about the indication for the treatment of DVT and secondary prevention in adult patients. If you have not prescribed Xarelto (rivaroxaban) for this indication, please check the response indicating that you do not prescribe for this indication.

Q16. What is the standard recommended dose for patients receiving Xarelto (rivaroxaban) for DVT treatment and secondary prevention?

(Check one.)

- ☐ 15 mg once a day for the first three weeks of administration, followed by 20 mg taken once a day
- ☐ 20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day
- ☐ 10 mg once a day
- ☐ 15 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day*
- ☐ None of the above
- ☐ I do not prescribe for this indication
- ☐ I don't know

Q17. What is the recommended dose for patients with moderate or severe renal impairment (creatinine clearance of 15-49 mL/min) receiving Xarelto (rivaroxaban) for DVT treatment and secondary prevention?

(Check one.)

- ☐ 20 mg, once a day
- ☐ 15 mg once a day for the first three weeks of administration, followed by 20 mg taken once a day
- ☐ 20 mg twice a day for the first three weeks of administration, followed by 20 mg taken once a day
- ☐ 10 mg once a day
- ☐ 15 mg twice a day for the first three weeks of administration, followed by 15 mg taken once a day*
- ☐ None of the above
- ☐ I do not prescribe for this indication
- ☐ I don't know

In this next section, please tell us about any information you have received about Xarelto (rivaroxaban).

Q18. Which of the following Xarelto (rivaroxaban) education material(s) have you received?

(Check all that apply.)

- ☐ Xarelto (rivaroxaban) Prescriber Guide
- ☐ Patient Card to provide to patients
- ☐ A company representative has discussed with me the proper use of and risks associated with Xarelto (rivaroxaban) for these indications
- ☐ The Summary of Product Characteristics for Xarelto (rivaroxaban) (SPC)
- ☐ Medical Publications
- ☐ None of the above

[PROGRAMMING NOTE: Fill with only those selected as being reviewed]

Q19. How helpful were these materials to you in treating and educating your patients?

	1 Not at all helpful	**2**	**3**	**4**	**5 Extremely helpful**
Xarelto (rivaroxaban) Prescriber Guide	☐	☐	☐	☐	☐
Patient Card	☐	☐	☐	☐	☐
Discussion with company representative	☐	☐	☐	☐	☐
Summary of Product Characteristics	☐	☐	☐	☐	☐
Publications	☐	☐	☐	☐	☐

Q20. In the past 6 months, for how many patients have you have prescribed Xarelto (rivaroxaban) in each of the following indications? If you have not written any prescriptions, please enter 0.

Indication	Number of patients for whom you have prescribed Xarelto (rivaroxaban) in the past 6 months	I do not prescribe for this indication	I don't know
SPAF		☐	☐
DVT treatment and secondary prevention		☐	☐

Q21. Of the patients for whom you have prescribed Xarelto (rivaroxaban) in the past 6 months, to what percentage did you provide a Patient Card?

Indication	Percentage of patients to whom you provided a Patient Card in the past 6 months	I do not prescribe for this indication	I don't know
SPAF		☐	☐
DVT treatment and secondary prevention		☐	☐

Q22. In which situations, if any, do you review and discuss the information on the patient card with your patients taking Xarelto (rivaroxaban)?

(Check all that apply.)

- ☐ When a patient is first prescribed Xarelto (rivaroxaban)
- ☐ When a patient is facing an invasive procedure
- ☐ When a patient has bleeding complications
- ☐ When a patient has a Xarelto (rivaroxaban) related adverse event
- ☐ I do not use the patient card
- ☐ I don't know

In this next section, please tell us a little about yourself and your clinical practice.

Q23. What is your physician specialty?

- ☐ General practitioner
- ☐ Neurologist
- ☐ Cardiologist
- ☐ Internist
- ☐ Haematologist
- ☐ Hospital stroke physician
- ☐ Emergency care
- ☐ Phlebologist
- ☐ Angiologist
- ☐ Other

Q24. When did you write your most recent prescription for Xarelto (rivaroxaban) for either of these indications?

(Check one.)

- ☐ Less than 1 month ago
- ☐ 1 to 3 months ago
- ☐ 4 to 6 months ago
- ☐ More than 6 months ago
- ☐ Not sure/don't remember

Q25. How many years have you been in clinical practice?

- ☐ 5 years or fewer
- ☐ 6 to 10 years
- ☐ 11 to 15 years
- ☐ 16 to 20 years
- ☐ 21 to 25 years
- ☐ More than 25 years

Q26. You are… ?

- ☐ Male
- ☐ Female

Q27. How would you characterise your practice?

- ☐ Individual private practice
- ☐ Group practice (single specialty)
- ☐ Group practice (multispecialty)
- ☐ University-based practice
- ☐ Hospital-based clinic
- ☐ Other

Thank you for completing the questionnaire.

Appendix D.
Patient Questionnaire

Xarelto Risk Minimisation Evaluation - Patient Questionnaire

Thank you for agreeing to participate in this study!

The entire questionnaire should take approximately 10 to 15 minutes to complete. Your responses will be kept completely confidential and will not be shared with your doctor or other health care professionals.

Please answer the following questions to confirm that you are eligible for this study.

Confirmatory Screening Questions

S1. Are you 18 years of age or older?

- ☐ Yes
- ☐ No (If no, please speak with the study coordinator to confirm your eligibility.)
- ☐ I don't know

S2. In the past 3 months, have you taken <u>Xarelto (rivaroxaban)</u>?

- ☐ Yes, I have taken Xarelto (rivaroxaban) in the past 3 months.
- ☐ No, I have not taken Xarelto (rivaroxaban) in the past 3 months. (If no, please speak with the study coordinator to confirm your eligibility.)
- ☐ I don't remember. (Please speak with the study coordinator to confirm your eligibility.)

S3. In the past 12 months, have you participated in a clinical research study (clinical trial) that assessed a treatment for the prevention of blood clots?

- ☐ Yes (Please speak with the study coordinator to confirm your eligibility.)
- ☐ No
- ☐ I don't know

Questionnaire

The purpose of the study is to learn more about patients' understanding of the important safety information related to Xarelto (rivaroxaban). For this reason we ask that you not look at the Xarelto (rivaroxaban) patient card while answering the following questions. The information gathered from this study will help to improve the communication about the safe use of Xarelto (rivaroxaban).

Note: An asterisk (*) indicates correct responses for review purposes.

Q1. Approximately how long ago were you first prescribed Xarelto (rivaroxaban)?

(Select the one most correct answer.)

- ☐ Less than 1 month
- ☐ 1 to 6 months
- ☐ 6 months to 1 year
- ☐ More than 1 year[1]
- ☐ Not sure/don't remember

Q2. Are you currently taking Xarelto (rivaroxaban)?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q3. Approximately how long have you been taking Xarelto (rivaroxaban)?

(Select the one most correct answer.)

- ☐ Less than 1 month
- ☐ 1 to 6 months
- ☐ 6 months to 1 year
- ☐ More than 1 year[1]
- ☐ Not sure/don't remember

[1] For the year 3 and year 7 assessments, the responses choices will be expanded appropriately. For example, in the year 3 assessment, this response will be changed to "1 to 2 years" and a new response "More than 2 years" will be added.

Q4. How many prescription medications are you currently taking, not including Xarelto (rivaroxaban)? If Xarelto (rivaroxaban) is the only medication that you are currently taking, please select "I am taking only Xarelto (rivaroxaban)."

(Select one most correct answer.)

- ☐ 1 to 2 prescription medication(s)
- ☐ 3 to 4 prescription medications
- ☐ 5 to 6 prescription medications
- ☐ Greater than 6 prescription medications
- ☐ I am taking only Xarelto (rivaroxaban)
- ☐ Not sure/don't remember

Q5. Before taking Xarelto (rivaroxaban), had you ever taken any prescription blood thinners (medications that thin the blood to prevent dangerous blood clots)?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q6. Where do you get most of your information about Xarelto (rivaroxaban)?

(Select the one most correct answer.)

- ☐ From my doctor's office
- ☐ From my pharmacy
- ☐ From a friend or family member
- ☐ From my caregiver (spouse, adult child, professional caregiver)
- ☐ From the Internet
- ☐ Other, specify _____

Risk Assessment

The following questions ask about the risks and side effect(s) that people who take Xarelto (rivaroxaban) could potentially experience. Please note these questions are just to learn more about your knowledge of these risks, not about your specific experiences while taking Xarelto (rivaroxaban).

Q7. Xarelto (rivaroxaban) is a prescription medicine used to…

(Select all that apply.)

- ☐ Reduce chronic pain
- ☐ Treat acid reflux or indigestion
- ☐ Thin the blood to prevent dangerous blood clots*
- ☐ None of the above
- ☐ I don't know

Q8. Has your doctor or other health care provider ever talked to you about the possible side effects of taking Xarelto (rivaroxaban)?

- ☐ Yes
- ☐ No
- ☐ I don't remember

Q9. Which of the following side effects can happen in people who are taking Xarelto (rivaroxaban)?

(Select all that apply.)

- ☐ Hair loss
- ☐ Tooth decay
- ☐ Abnormal bleeding*
- ☐ None of the above
- ☐ I don't know

Q10. Which of the following are some of the signs or symptoms of bleeding while taking Xarelto (rivaroxaban)?

(Select Yes, No, or I don't know for each possible sign or symptom listed below.)

Possible Sign or Symptom	**Yes,** this is a sign or symptom of bleeding when taking Xarelto (rivaroxaban)	**No,** this is **NOT** a sign or symptom of bleeding when taking Xarelto (rivaroxaban)	**I don't know**, if this is a sign or symptom of bleeding when taking Xarelto (rivaroxaban)
Swelling or Discomfort	☐ Yes*	☐ No	☐ I don't know
Pain	☐ Yes*	☐ No	☐ I don't know
Intense Hunger	☐ Yes	☐ No*	☐ I don't know
Headache, dizziness, or weakness	☐ Yes*	☐ No	☐ I don't know
Unusual bruising, nosebleeds, or bleeding of the gums	☐ Yes*	☐ No	☐ I don't know
Bleeding that takes a long time to stop	☐ Yes*	☐ No	☐ I don't know
Menstrual or vaginal bleeding that is heavier than normal	☐ Yes*	☐ No	☐ I don't know
Pink or brown urine	☐ Yes*	☐ No	☐ I don't know
Black or red stools	☐ Yes*	☐ No	☐ I don't know
Coughing up or vomiting blood or material that looks like coffee grounds	☐ Yes*	☐ No	☐ I don't know

Safe Use

Q11. Please read each of the following statements and then select Yes, No, or I don't know for each statement.

Statement	**Yes**, this is true	**No**, this is false	**I don't know**
Q11a. I can stop taking Xarelto (rivaroxaban) at any time without consulting with my doctor.	☐ Yes	☐ No*	☐ I don't know
Q11b. I need to speak to my health care provider prior to any intake of other medication(s).	☐ Yes*	☐ No	☐ I don't know
Q11c. I need to inform my health care provider about Xarelto (rivaroxaban) intake prior to any kind of surgery or invasive procedure.	☐ Yes*	☐ No	☐ I don't know
Q11d. Before taking Xarelto (rivaroxaban), I need to tell my health care provider about any abnormal bleeding conditions I may have.	☐ Yes*	☐ No	☐ I don't know

Q12. How should you take Xarelto (rivaroxaban) 15 mg or 20 mg?

(Select one.)

- ☐ With food*
- ☐ On an empty stomach
- ☐ I don't know

Q13. What should you do to ensure optimal protection from blood clots?

(Select all that apply.)

- ☐ Take Xarelto (rivaroxaban) exactly as prescribed by your doctor*
- ☐ Take Xarelto (rivaroxaban) only when you do not feel good
- ☐ Never skip a dose of Xarelto (rivaroxaban)*
- ☐ I don't know

Actions to Take

Q14. What should you do if you have any signs or symptoms of bleeding that could be related to Xarelto (rivaroxaban)?

(Select the correct answer)

- ☐ Stop taking Xarelto (rivaroxaban)
- ☐ Tell my health care provider right away*
- ☐ Skip one dose and see if the sign or symptom goes away
- ☐ Drink water to help wash the medication out of my system
- ☐ None of the above
- ☐ I don’t know

Patient Card Receipt and Review

Now we are going to ask you some questions about the Patient Card (also called "Alert Card") that you may have received from your health care provider. This small, pocket-sized card contains important safety information about Xarelto (rivaroxaban). A picture of the front of the card is provided below.

Q15. Have you <u>ever</u> received or gotten a Patient Card for Xarelto (rivaroxaban)?

- ☐ Yes [GO TO Q16]
- ☐ No [SKIP TO Q21]
- ☐ I don't remember [SKIP TO Q16]

Answer questions Q14 – Q19 only if you received a Patient Card for Xarelto (rivaroxaban)

Q16. How often do you keep the Patient Card with you?

(Select one.)

- ☐ All the time
- ☐ Most of the time
- ☐ Some of the time
- ☐ Rarely
- ☐ Never
- ☐ I don't remember

Q17. Who do you present the Patient Card to…

(Select one.)

- ☐ Every physician or dentist prior to treatment
- ☐ No one, it is just for my information
- ☐ Only to my doctor, if he or she asks for it
- ☐ I don't remember

Q18. Have you ever read the Patient Card for Xarelto (rivaroxaban)?

- ☐ Yes [SKIP TO Q20]
- ☐ No [GO TO Q19]
- ☐ I don't remember [GO TO Q19]

Q19. Why haven't you ever read the Patient Card for Xarelto (rivaroxaban)?

(Select all that apply.)

[ALL RESPONSES GO TO Q21]

- ☐ I haven't taken the medication yet
- ☐ Someone else explained it to me
- ☐ I lost the patient card
- ☐ I already knew the information
- ☐ I typically do not read the materials given to me by my doctor
- ☐ Other

Q20. How much of what you read in the Patient Card did you understand?

(Select one.)

- ☐ All of it
- ☐ Most of it
- ☐ Some of it
- ☐ None of it

Q21. Has someone else *explained* the information in the Patient Card for Xarelto (rivaroxaban) to you?

(Select all that apply.)

- ☐ Yes, a doctor
- ☐ Yes, a nurse or physician assistant
- ☐ Yes, a pharmacist or someone at the pharmacy
- ☐ Yes, a friend, family member, or caregiver
- ☐ No
- ☐ I don't remember

Q22. Did you look at the Patient Card just before or while you were completing this questionnaire?

- ☐ Yes
- ☐ No

Demographics

In this last section, please tell us a little information about yourself to help us describe the participants completing this questionnaire.

Q23. I was prescribed Xarelto (rivaroxaban) for the following reason(s)…

(Select all that apply.)

- ☐ Prevention of stroke
- ☐ A blood clot in a vein
- ☐ I don't know
- ☐ Other _____

Q24. How old are you?

- ☐ 18-25 years
- ☐ 26-35 years
- ☐ 36-45 years
- ☐ 46-55 years
- ☐ 56-65 years
- ☐ 66-75 years
- ☐ 76-85 years
- ☐ > 85 years

Q25. You are…?

- ☐ Male
- ☐ Female

Q26. What is the highest level of education you have completed? (Select one.)

- ☐ No schooling completed
- ☐ Primary school
- ☐ Secondary school
- ☐ Some college
- ☐ University – Bachelor's degree
- ☐ University – Master's degree
- ☐ Professional degree (e.g., MD, LLB)
- ☐ Doctorate degree (e.g., PhD)

Thank you again for taking time to participate in this study! Your answers are very important. If you have any questions about how to safely take Xarelto (rivaroxaban) or about the risks associated with Xarelto (rivaroxaban), you should talk with your doctor or pharmacist.

Please place and seal your completed questionnaire in the envelope provided to you by the study coordinator. Also, be sure and let the study coordinator know you have finished so that you can be compensated for your time!