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

Protocol, Version 2.0

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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.

1. 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.

2. 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 alert 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 alert card and counselling about the details of the patient alert card

The patient alert 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 alert 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. The status of these assessments will be presented regularly in periodic safety update reports. The five countries to be included in the study are the United Kingdom (UK), Germany, France, Italy, and Spain. Due to drug approval delays in Italy, the 18-month assessment will not include Italy. Therefore, data will be collected from four countries in the 18-month assessment (UK, Germany, France, and Spain).

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 alert 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 alert card and determine if the patients use and carry the patient alert 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 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 a physician panel and/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[1], 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

[1] Due to drug approval delays in Italy, the 18-month assessment will not include Italy. Therefore, the total sample size for the 18-month assessment will be 1,200 physicians.

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 alert card and counselling about the details of the patient alert 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 alert 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. The physician questionnaire has been cognitively tested with physicians in each of the target countries. Section 3.3 provides a detailed description of the cognitive pretesting process. Modifications have been made to the questionnaire based on the pretesting results and additional feedback from the sponsor. The final version of the questionnaire can be found in Appendix C. Some modifications 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 made via e-mail or issued by phone 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 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[1], to allow reasonable precision around estimates of patients' knowledge and understanding of the patient alert 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

[1] Due to drug approval delays in Italy, the 18-month assessment will not include Italy. Therefore, the total sample size for the 18-month assessment will be 400 patients.

Patient Sample Size	Intraclass Correlation Coefficient[a]	Correct Response (%)	Lower 95% Confidence Limit (%)	Upper 95% Confidence Limit (%)
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 has been cognitively tested with patients in each of the target countries. Modifications have been made to the questionnaire based on the results of testing and additional feedback from the sponsor. The final version of the questionnaire can be found in Appendix D. Some modifications to the questionnaire are anticipated based on country-specific requirements. The questionnaire will assess patient knowledge of the following concepts:

- Receipt and use of the patient alert card
- Knowledge of the key safety messages outlined in the patient alert 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 alert 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 approximately 20 minutes to complete.

3.2.6 Patient Data Collection

The patient questionnaire will be self-administered (closed-ended questions with predefined answers) on hard copy forms 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 be asked to complete the questionnaire without referring to the patient alert card. Once they have completed the questionnaire, the patient will be asked to review the patient alert card and then re-answer selected questions related to key safety information to gather data on patient knowledge immediately after exposure to the card. Patients will then place their completed forms 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 in preparation for fielding the study, RTI Health Solutions (RTI-HS) conducted 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 asked pretest participants to complete the questionnaires while thinking aloud or describing their thought processes as they answer the questionnaire items. Pretest interviewers used an interview guide that included 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 helped to identify problems with questionnaire items, wording, response choices, etc., and ensured that participants understand the questions. The pretest interview data were used to optimise the language used in the questionnaires prior to fielding the patient and physician assessments. Likewise, the cognitive testing helped to identify cultural or translational issues with the draft questionnaires so that they could be modified to meet the individual needs of each country while maintaining comparability across the study. The pretest interviews also provided 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 was conducted with 25 physicians across the five countries who prescribe rivaroxaban for SPAF or DVT treatment and secondary

prevention. Additionally, cognitive pretesting of the patient questionnaire was conducted with 25 patients across the five countries who were being treated for SPAF or DVT/PE. Changes to both questionnaires were made based on the results of the cognitive testing and additional feedback from the sponsor. In addition, the patient questionnaire will now include re-administration of selected questions to evaluate patients' understanding of key safety information following exposure to the patient alert card.

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 interviewers completed safety training, which included instructions to complete an ADR case report form and submit it to the BHC pharmacovigilance country head (PVCH) if a spontaneous ADR was reported.

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 patient's physician directly, if BHC determines that follow-up is needed and if the reporting patient has given consent for his/her physician 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 for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2012).
- The study will be reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checkl*ist (*http://www.strobe-statement.org/index.php?id=available-checklists).
- This study will comply with the European Medicines Agency (EMA)'s *Guideline on Good Pharmacovigilance Practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products* (EMA, 2012b).

- The study will comply with the definition of a non-interventional (observational) study provided i*n the EMA's Guideline on Good Pharmacovigilance Practices (GVP): Module VIII – Post-Authorisation Safety Studies* (EMA, 2012a).

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 alert card, awareness of the key information contained in the patient alert card, and whether the patient carries the patient alert 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 alert card, and provider knowledge.

The study will target a total of 1,500 physicians[1] (approximately 300 per country) and 500 patients[2] (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.

[1] Due to drug approval delays in Italy, the 18-month assessment will not include Italy. Therefore, the total sample size for the 18-month assessment will be 1,200 physicians.

[2] Due to drug approval delays in Italy, the 18-month assessment will not include Italy. Therefore, the total sample size for the 18-month assessment will be 400 patients.

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

297 mm

NOW UPDATED AND INCLUDES A NEW INDICATION

XARELTO® ▼ (RIVAROXABAN) EDUCATIONAL PACK

FOR 15MG AND 20MG DOSING

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors*

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

211 mm

* Such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack

** Xarelto is not recommended for haemodynamically unstable PE patients

Xarelto® rivaroxaban

Prescribing Information can be found on pages 10 and 11

Bayer HealthCare

Date of preparation: November 2012
L.GB.10.2012.07818

DO NOT PRINT GUIDES

297 mm

211 mm

Bayer HealthCare have designed this educational pack to support you in the appropriate prescribing of Xarelto. It contains important information specifically relating to 15mg and 20mg dosing of Xarelto, for use in stroke prevention in AF and treatment of DVT and PE.

Within this pack you will find a:

- Prescriber guide
- Summary of product characteristics (SmPC)
- Patient alert card

If you would like to order more copies of the Xarelto educational pack, please visit **www.xarelto-info.co.uk**

Alternatively, please contact Bayer Medical Information at **medical.information@bayer.co.uk** or call **01635 563116.**

DO NOT PRINT GUIDES

NOW UPDATED AND INCLUDES A NEW INDICATION

XARELTO® (RIVAROXABAN) PRESCRIBER GUIDE FOR 15MG AND 20MG DOSING

Xarelto® ▼
rivaroxaban

Prescribing information can be found on pages 10 and 11

This guide is to be used to support the appropriate use of Xarelto in eligible atrial fibrillation (AF) patients and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

It includes the following information:

- **Indications**
- **Dosing recommendations**
- **Populations potentially at higher risk of bleeding**
- **Perioperative management**
- **Overdose**
- **How to manage bleeding complications**
- **Coagulation testing**

Xarelto patient alert card

You must provide a patient alert card to each patient who is prescribed Xarelto 15mg or 20mg.

Please explain the implications of anticoagulant treatment to patients, in particular highlighting the need for:

- treatment compliance
- taking medication with food
- signs or symptoms of bleeding
- when to seek medical attention.

The patient alert card will inform treating physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information.

Please instruct patients to carry the patient alert card with them at all times and present it to every health care provider.

INDICATIONS

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.

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults. (See section 4.4 of the SmPC for haemodynamically unstable PE patients).

DOSING RECOMMENDATIONS

Xarelto 15mg and 20mg must be taken with food to ensure sufficient absorption of the drug. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

Note: Xarelto is also available at a 10mg dose for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. This dose can be taken with or without food.

Dosing in patients with AF

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

*In patients with moderate or severe renal impairment the recommended dose is 15mg 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 15mg once daily. Xarelto is to be used with caution in patients with severe renal impairment as limited clinical data indicates a significantly increased plasma concentration. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

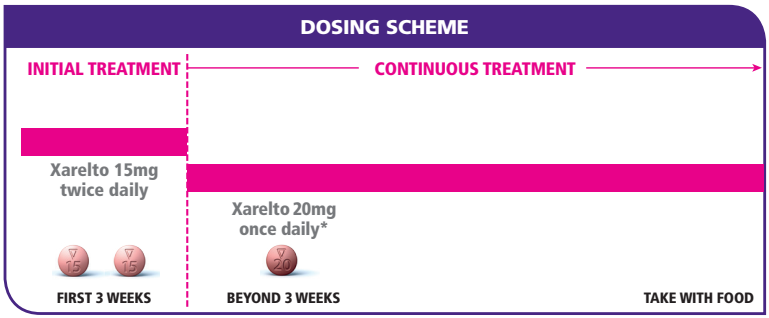
Xarelto should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

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 treatment of DVT and PE, and prevention of recurrent DVT and PE in adults

Patients are initially treated with 15mg **twice daily** for the first three weeks. This initial treatment is followed by 20mg **once daily** for the continued treatment period.



* Patients with DVT/PE and renal impairment

Patients with renal impairment

Patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE do not require a dose reduction.

However, during the continuous treatment phase, a reduction of the dose from 20mg once daily to 15mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15mg is based on PK modelling and has not been studied in this clinical setting.

The use of Xarelto 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. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

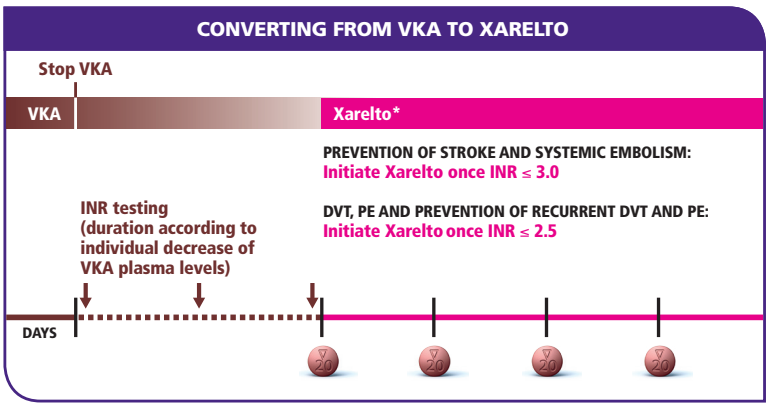
Missed dose:

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

CONVERTING FROM VITAMIN K ANTAGONISTS (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 international normalised ratio **(INR)** is ≤ **3.0**.

For patients treated for **DVT, PE 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**.



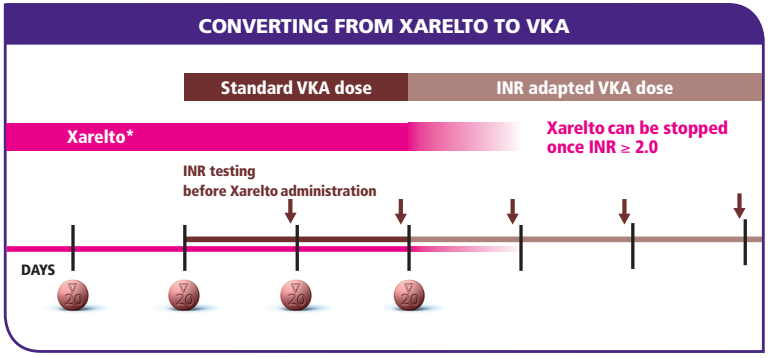
*See dosing recommendations for required daily dose

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 minimising the risk of bleeding during conversion of therapy.

When converting to VKA, Xarelto and VKA should overlap 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 has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

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 Low Molecular Weight Heparin (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 at the time the next Xarelto dose would have been taken.

POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Like all anticoagulants, Xarelto may increase the risk of bleeding.

Therefore Xarelto is contraindicated in patients:

- with clinically signficant active bleeding.
- with a lesion or condition at significant risk of major bleeding such as current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or supected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, dabigatran, apixaban etc) except under the circumstances of switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Xarelto is contraindicated during pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto. Xarelto is contraindicated during breastfeeding. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

SEVERE SUB-GROUPS OF PATIENTS

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

Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding.

- *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. Use of Xarelto is not recommended in patients with creatinine clearance <15 ml/min.
- *Patients concomitantly receiving other medicinal products:*
  - Use of Xarelto is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir).
  - Take care with drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid, or platelet aggregation inhibitors.

- *Patients with other haemorrhagic risk factors:*

  As with other antithrombotics, Xarelto is not recommended in patients with an increased bleeding risk such as:

  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - other gastrointestinal disease that can potentially lead to bleeding complications
  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Xarelto 15/20mg 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 due to Xarelto should be assessed against the urgency of the intervention.

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

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Xarelto and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving Xarelto, the next Xarelto administration should be delayed or treatment discontinued as appropriate. Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and 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. However, measuring Xarelto levels may be useful in exceptional situations where knowledge of Xarelto exposure may help to make clinical decisions, e.g. overdose and emergency surgery.

Anti-FXa assays with Xarelto-(rivaroxaban) specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated haemostatic status can also be assessed by PT using Neoplastin as described in the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR 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.

Xarelto® ▼10 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 10 mg rivaroxaban tablet. **Indication(s):** Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. **Posology and method of administration:** Dosage 10 mg rivaroxaban orally once daily with or without food; initial dose should be taken 6 to 10 hours after surgery provided haemostasis established. *Recommended treatment duration:* Dependent on individual risk of patient for VTE determined by type of orthopaedic surgery: for major hip surgery 5 weeks; for major knee surgery 2 weeks. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** Mild & moderate (creatinine clearance 50-80ml/min & 30-49 ml/min respectively) – no dose adjustment necessary; severe (creatinine clearance 15-29ml/min) - limited data indicates rivaroxaban concentrations are significantly increased, use with caution. Patients with creatinine clearance < 15ml/min – use not recommended. ***Hepatic impairment:*** Do not use in patients with hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications**: Hypersensitivity to active substance or any excipient; clinically significant active bleeding; hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings and precautions:** Not recommended in patients: undergoing hip fracture surgery; in patients receiving concomitant systemic treatment with strong CYP3A4 and P-gp inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with severe renal impairment (creatinine clearance <15 ml/min). Increased risk of bleeding therefore careful monitoring for signs/symptoms of bleeding complications & anaemia required after treatment initiation: in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min); or with moderate renal impairment (creatinine clearance 30 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostasis; in patients with congenital or acquired bleeding disorders; uncontrolled severe arterial hypertension; active ulcerative gastrointestinal disease (consider appropriate prophylactic treatment for at risk patients); 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. If clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Take special care when neuraxial anaesthesia or spinal/epidural puncture is employed due to risk of epidural or spinal haematoma with potential neurologic complications. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as increased rivaroxaban plasma concentrations to a clinically relevant degree are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations.. **Pregnancy and breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse events like syncope and dizziness are common. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, syncope, eye haemorrhage, tachycardia, hypotension, haematoma, epistaxis, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, pain in extremity, urogenital tract haemorrhage, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, cutaneous & subcutaneous, haemoptysis, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), abnormal hepatic function, renal impairment; hyperbilirubinaemia, jaundice, pseudoaneurysm formation following percutaneous intervention. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** 10 tablets: £21.00, 30 tablets: £63.00 and 100 tablets: £210.00. **MA Number(s):** EU/1/08/472/001-10 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. **Date of preparation:** June 2012.

Xarelto® is a trademark of the Bayer Group.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Bayer plc. Tel: 01635 563500, Fax: 01635 563703, Email: phdsguk@bayer.co.uk

Xarelto® ▼15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 15mg/20mg rivaroxaban tablet **Indication(s):** 1. Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *Dosage 1 (SPAF):* 20 mg orally *o.d.* with food. *Dosage 2 (DVT & PE):* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; take with food. Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment necessary; moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29 ml/min; limited data indicates rivaroxaban plasma concentrations are significantly increased, use with caution) – *SPAF:* reduce dose to 15mg *o.d.*, DVT & PE: 15 mg *b.i.d.* for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg o.d. if patient's bleeding risk outweighs risk for recurrent DVT & PE; Patients with creatinine clearance <15 ml/min - use not recommended. ***Hepatic impairment:*** Do not use in patients with hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C patients. ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; clinically significant active bleeding; lesion or condition at significant risk of major bleeding (refer to SmPC); concomitant treatment with any other anticoagulant agent except under the circumstances of switching therapy to or from rivaroxaban or when unfractionated heparin is given at doses necessary to maintain a patent central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings & precautions:** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. Following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation. Use with caution- in patients with severe renal impairment or with renal impairment concomitantly receiving potent inhibitors of CYP3A4 (PK models show increased rivaroxaban concentrations); in patients treated concomitantly with medicines affecting haemostasis. Use is not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established. See SmPC for full details. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as increased rivaroxaban plasma concentrations to a clinically relevant degree are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving other anticoagulants, NSAIDs or platelet aggregation inhibitors due to the increased bleeding risk. Strong CYP3A4 inducers should be used concomitantly with caution as they may reduce rivaroxaban plasma concentrations. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and use machines:** Adverse reactions like syncope (uncommon) & dizziness (common). Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, allergic reactions, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, abnormal hepatic function, hyperbilirubinaemia, jaundice, vascular pseudoaneurysm. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** *15mg* – 28 tablets: £58.80, 42 tablets: £88.20, 100 tablets: £210.00; *20mg* – 28 tablets: £58.80, 100 tablets £210.00 **MA Number(s):** EU/1/08/472/011-21 **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA, U.K. Telephone: 01635 563000. Date of preparation: November 2012.

Xarelto® is a trademark of the Bayer Group.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Bayer plc. Tel: 01635 563500, Fax: 01635 563703, Email: phdsguk@bayer.co.uk

Bayer HealthCare

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L.GB.10.2012.0781

Appendix B.
Xarelto Patient Alert Card

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.

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®15mg and 20mg must be taken with food.

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PATIENT ALERT CARD

Xarelto® 15mg
Xarelto® 20mg

- **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: _____

Blood type: _____

Weight: _____

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

Physician Questionnaire

Xarelto Risk Minimization Study

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 HealthCare (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). This is not a marketing survey, but a scientific study conducted at the request of the European Medicines Agency (EMA), the drug regulatory body in the European Union (EU). The purpose of the study is to assess prescribers' understanding of and compliance with the safe use of Xarelto for the following two chronic indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- Treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism following an acute deep vein thrombosis in adults. (This indication will be referred to as "**deep vein thrombosis 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 which takes 10 to 15 minutes to complete is being administered to approximately 1,200 physicians across several countries within the EU. Your answers will be treated with strict confidentiality. Any information provided will only be evaluated together with that of other respondents.

By completing and submitting this survey, you indicate that you have read the information provided above and voluntarily agree to participate in this study.

[The survey will be programmed online and a link will be provided to a contact page which will include the phone number for RTI's Office of Human Research Protection should participants have a question about their rights as a study participant.]

C1. Do you agree to participate in the study?

☐ Yes, I agree to participate in this study.
☐ No, I do not agree to participate in this study.

[IF C1 = "No, I do not agree to participate in this study.",

THEN DISPLAY "You have indicated that you do not agree to participate in the study. Thank you for your time." TERMINATE SURVEY].

To confirm your eligibility to participate in this brief assessment, please answer the following question:

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

(Tick all that apply.)

- ☐ Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- ☐ Deep vein thrombosis treatment and secondary prevention in adults
- ☐ I have not prescribed Xarelto for either of these indications

[IF S1 = "I have not prescribed Xarelto for either of these indications",
THEN DISPLAY "It does not appear that you qualify for the survey. Thank you for your time and interest." AND TERMINATE SURVEY
ELSE DISPLAY "We have confirmed that you are eligible. We will now continue with the survey questions].

Physician Questionnaire

This questionnaire is designed to gain a better understanding of prescribers' knowledge about Xarelto for only the following two approved indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation
- Deep vein thrombosis treatment and secondary prevention

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

The first set of questions asks about your prescribing practices.

Q1. In the past 6 months, for how many patients have you prescribed Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation?

- ☐ 1 to 10
- ☐ 11 to 20
- ☐ 21 or more
- ☐ I have not prescribed Xarelto for this indication

Q2. In the past 6 months, for how many patients have you prescribed Xarelto for deep vein thrombosis treatment and secondary prevention?

- ☐ 1 to 10
- ☐ 11 to 20
- ☐ 21 or more
- ☐ I have not prescribed Xarelto for this indication

Q3. When did you write your <u>most recent</u> prescription for Xarelto for either of these indications?

(Tick one.)

- ☐ Less than 1 month ago
- ☐ 1 to 3 months ago
- ☐ 4 to 6 months ago
- ☐ I don't know

Q4. Which of the following Xarelto treatment activities are you responsible for?

(Tick all that apply.)

- ☐ I initiate Xarelto treatment or convert treatment from or to Xarelto
- ☐ I write follow up (maintenance) prescriptions for Xarelto

The next questions ask about the use of Xarelto for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and deep vein thrombosis treatment and secondary prevention.

Q5. What is the most important risk associated with taking Xarelto?

(Tick one.)

- ☐ Neoplasia
- ☐ Hypertension
- ☐ Risk of bleeding
- ☐ Immunosuppression
- ☐ I don't know

Q6. Which of the following populations are at an increased risk of experiencing serious side effect(s) associated with Xarelto?

(Tick 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			
Patients taking products that affect hemostasis such as NSAIDS, acetylsalicylic acid, platelet aggregation inhibitors	☐	☐	☐
Patients at risk of bleeding	☐	☐	☐
Patients with chronic constipation	☐	☐	☐

Q7. To which patient groups is Xarelto contraindicated?

(Tick all that apply.)

- ☐ Patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh class B and C
- ☐ Patients who are pregnant or breastfeeding
- ☐ Patients receiving concomitant treatment with any other anticoagulant such as unfractionated heparin (UFH), low molecular weight heparins, heparin derivatives or oral anticoagulants except when switching therapy to or from Xarelto or when UFH is given at doses necessary to maintain a patent central venous or arterial catheter
- ☐ Patients with clinically significant active bleeding
- ☐ I don't know

Q8. Xarelto (15 or 20 mg) must be taken….?

(Tick one.)

- ☐ On an empty stomach
- ☐ With food/on a full stomach
- ☐ I don't know

Q9. Is routine coagulation monitoring required for patients taking Xarelto for these indications?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q10. In which of the following situations is INR monitoring needed?

(Tick all that apply.)

- ☐ When converting from vitamin K antagonist (VKA) (e.g., warfarin) to Xarelto
- ☐ When converting from Xarelto to VKA
- ☐ Continual INR monitoring is required for all patients taking Xarelto
- ☐ I don't know

Q11. Which of the following steps should be taken when converting patients from VKA (e.g., warfarin) to Xarelto?

(Tick all that apply.)

- ☐ Stop VKA without measuring INR
- ☐ For patients treated for prevention of stroke and systemic embolism, stop VKA and initiate Xarelto when INR is ≤ 3
- ☐ For patients treated for deep vein thrombosis and secondary prevention, stop VKA and initiate Xarelto when INR is ≤ 2.5
- ☐ I don't know

Q12. Which of the following steps should be taken when converting patients from Xarelto to VKA (e.g., warfarin)?

(Tick all that apply.)

- ☐ Overlap the two drugs until INR is ≥ 2.0
- ☐ Measure INR but make sure it has been longer than 24 hours since the last dose of Xarelto
- ☐ Stop Xarelto at any time
- ☐ Measure INR at any time of the day
- ☐ I don't know

Q13. Which of the following are true when converting from parenteral anticoagulants to Xarelto…?

(Tick all that apply.)

- ☐ Stop parenteral anticoagulants for a week prior to starting Xarelto
- ☐ For patients with continuously administered parenteral anticoagulants such as intravenous unfractionated heparin, Xarelto should be started at time of drug discontinuation
- ☐ For patients with parenteral drug on a fixed dosing scheme such as low molecular weight heparin (LMWH), Xarelto should be started 0 to 2 hours before the next scheduled drug administration
- ☐ I don't know

Q14. If an invasive procedure or surgical intervention is required, when should treatment with Xarelto (15 to 20 mg) be suspended (if possible, based upon clinical judgement of physician)?

(Tick one.)

- ☐ One week prior to the procedure or surgical intervention
- ☐ At least 24 hours prior to the procedure or surgical intervention
- ☐ It is not necessary to stop Xarelto for these procedures
- ☐ I don't know

Q15. What are the most appropriate actions you should take if a patient taking Xarelto presents with a medically important bleeding complication?

(Tick all that apply.)

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

[IF Q1 = "I have not prescribed Xarelto for this indication", SKIP TO intro text preceding Q18.

The following questions are about the indication for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Q16. What is the standard recommended dose of Xarelto for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation?

(Tick one.)

- ☐ 20 mg taken once a day
- ☐ 15 mg taken once a day
- ☐ 10 mg taken once a day
- ☐ None of the above
- ☐ 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 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation?

(Tick one.)

- ☐ 20 mg taken once a day
- ☐ 15 mg taken once a day
- ☐ 10 mg taken once a day
- ☐ None of the above
- ☐ I don't know

[IF Q2 = "I have not prescribed Xarelto for this indication", SKIP TO intro text preceding Q19.

The following questions are about the indication for deep vein thrombosis treatment and secondary prevention in adult patients.

Q18. What is the standard recommended dose for patients receiving Xarelto for deep vein thrombosis treatment and secondary prevention?

(Tick one.)

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

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

Q19. From which of the following sources did you receive information about Xarelto?

(Tick all that apply.)

- ☐ Xarelto Prescriber Guide
- ☐ Briefing from a company representative
- ☐ Discussion with a clinical expert
- ☐ The Summary of Product Characteristics for Xarelto
- ☐ Clinical trials published in the medical literature
- ☐ Other
- ☐ None of the above

Q20. How helpful were these sources to you in treating and educating your patients?

[ONLY DISPLAY RESPONSES THAT WERE CHECKED IN Q19; IF Q19 = "NONE OF THE ABOVE", SKIP TO Q21.]

	1 Not at all helpful	2	3	4	5 Extremely helpful
Xarelto Prescriber Guide	☐	☐	☐	☐	☐
Briefing from a company representative	☐	☐	☐	☐	☐
Discussion with a clinical expert	☐	☐	☐	☐	☐
Summary of Product Characteristics	☐	☐	☐	☐	☐
Medical Publications	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐

Q21. Have you received Xarelto Patient Alert Cards to provide to your patients?

☐ Yes
☐ No

[IF Q21 IS NO, SKIP TO Q23.]

Q22. Considering the Xarelto patients under your care, to how many did you provide a Patient Alert Card?

☐ Every one of my patients
☐ Most of my patients
☐ A few of my patients
☐ None of my patients

Q23. When would you discuss the information on the Patient Alert Card with your patients taking Xarelto?

(Tick all that apply.)

- ☐ When first prescribing Xarelto
- ☐ When a patient is facing an invasive procedure or surgical intervention
- ☐ When a patient has bleeding complications
- ☐ When a patient has a Xarelto related adverse event
- ☐ I do not use the Patient Alert Card
- ☐ Other

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

Q24. Which of the following <u>best</u> describes your specialty?

- ☐ General medicine
- ☐ Neurology
- ☐ Cardiology
- ☐ Haematology
- ☐ Accident & Emergency medicine
- ☐ Oncology
- ☐ Other

Q25. How many years have you been practicing medicine?

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

Q26. Are you…?

- ☐ Male
- ☐ Female

Q27. How would you characterise your practice?

(Tick all that apply.)

- ☐ General practice
- ☐ Hospital-based clinic
- ☐ Nursing home
- ☐ Other

Thank you for completing the questionnaire!

In order to continue to monitor and evaluate the safety of Bayer products, the sponsor is interested in any adverse events that have not already been reported. If you have any such adverse events to report for your patients, please do so using the contact information provided here.

[Contact information will be inserted in the survey or on the contact page.]

If you would like additional information or have any questions about the prescribing guidelines or safety information related to Xarelto, please click to the link below to access the Xarelto Prescriber Guide.

[INSERT LINK]

Appendix D.
Patient Questionnaire

Xarelto Risk Minimization Study

Survey Instructions

Thank you for agreeing to participate in this study!

Taking part in this study will take approximately 20 to 25 minutes of your time. Your responses will be kept completely confidential and will not be shared with your health care professionals (e.g., surgery or hospital based doctor or nurse).

This survey consists of two questionnaires. Please follow the instructions below to complete the survey. If you have any questions, please ask the study coordinator for help.

Step 1 - Open envelope #1 and complete the first questionnaire. Please do not refer to the Xarelto patient alert card or other Xarelto educational materials while answering the questionnaire.

Step 2 – When you have completed the first questionnaire, place it back into the envelope and seal the envelope.

Step 3 – Open envelope #2. Inside the envelope you will find a Xarelto patient alert card. Please read the Xarelto patient alert card. After you have read it, complete the second questionnaire.

Step 4 - When you have completed the second questionnaire, place it back into the envelope and seal the envelope.

Step 5 – Return both envelopes to the study coordinator.

Xarelto Risk Minimization Study

Patient Questionnaire #1

This is the first of two questionnaires. Please complete this questionnaire before moving on to the second questionnaire (found in a separate envelope).

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

S1. Are you 18 years of age or older?

- ☐ Yes
- ☐ No (If no, please speak with the study coordinator to confirm your eligibility.)

S2. Have you taken Xarelto (also known as rivaroxaban) in the past 3 months?

- ☐ Yes, I have taken Xarelto in the past 3 months
- ☐ No, I have not taken Xarelto in the past 3 months
- ☐ I don't know

The purpose of this study is to learn more about your knowledge and understanding of the safety information related to Xarelto (rivaroxaban).

Please do <u>not</u> look at the Xarelto patient alert card while answering the following questions.

Q1. Are you currently taking Xarelto?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q2. Approximately how long have you been taking Xarelto?

Select the <u>one</u> answer that best applies to you.

- ☐ Less than 1 month
- ☐ Between 1 and 6 months
- ☐ More than 6 months but less than 1 year
- ☐ More than 1 year
- ☐ I don't know

Q3. How many prescription medications, including Xarelto, are you currently taking on a regular basis?

Select the <u>one</u> answer that best applies to you.

- ☐ I am taking only 1 prescription medication (Xarelto)
- ☐ 2 prescription medications
- ☐ 3 to 4 prescription medications
- ☐ 5 to 6 prescription medications
- ☐ More than 6 prescription medications
- ☐ I don't know

Q4. Xarelto is a prescription medicine used to thin the blood to prevent blood clots?

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

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

- ☐ Yes

- ☐ No
- ☐ I don't know

Q6. Where did you get <u>most</u> of your information about Xarelto?

Select the <u>one</u> answer that best applies to you.

- ☐ From my doctor
- ☐ From a specialist at the hospital
- ☐ From my pharmacist
- ☐ From a friend or family member
- ☐ From my carer
- ☐ From articles in newspapers or magazines
- ☐ From the Internet
- ☐ From the Xarelto Patient Alert Card and/or patient information leaflet

Other, please specify _____

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

The following questions are to learn more about your knowledge of side effect(s) that people who take Xarelto could potentially experience.

Please note that these questions are not asking about your own experiences while taking Xarelto.

If you have any questions or concerns about the information in the questionnaire, please talk with your health care professional.

Q7. Has your health care professional ever talked to you about the possible side effects of Xarelto?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q8. Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q9. Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and <u>not</u> about your own experience.

Check the box Yes, No, or I don't know for each of the following items.

	Yes, this **<u>may be</u>** a sign or symptom of bleeding when taking Xarelto	**No,** this is **<u>not</u>** a sign or symptom of bleeding when taking Xarelto	**<u>I don't know</u>** if this is a sign or symptom of bleeding when taking Xarelto
Pain	☐	☐	☐
Swelling or discomfort	☐	☐	☐
Headache, dizziness, or weakness	☐	☐	☐
Unusual bruising	☐	☐	☐

Q10. I must <u>not</u> stop taking Xarelto at any time without consulting with my doctor.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q11. I need to speak to my doctor prior to any intake of other medication(s).

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q12. I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q13. I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q14. Should Xarelto (15 mg and 20 mg tablets) be taken with food?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q15. What should you do to ensure Xarelto is effective in preventing blood clots?

Select <u>all</u> that apply.

- ☐ Take Xarelto exactly as prescribed by your Health Care Professional
- ☐ Take Xarelto only when you do not feel well
- ☐ Do not miss a dose of Xarelto
- ☐ I don't know

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

Q16. I was prescribed Xarelto for the following reason(s)…

Select <u>all</u> that apply

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

Q17. 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
- ☐ 86 years or older

Q18. Are you …?

- ☐ Male
- ☐ Female

Q19. What is the highest level of education you have completed?

Select the one answer that best applies to you.

- ☐ Primary school education or less
- ☐ Secondary school education (e.g. GCSE/A level, Scottish Standard Grades/Highers)
- ☐ Professional or work-related college qualifications (e.g. Certificate of Higher Education, Diploma of Higher Education, foundation degree)
- ☐ Undergraduate university degree (e.g. BSc/BA)
- ☐ Postgraduate university degree (e.g. MSc/MA, MPhil, PhD)

You have now reached the end of the first questionnaire. Please place your completed questionnaire back into the envelope and seal the envelope. Then, follow the instructions for completion of the second part of the survey.

Xarelto Risk Minimization Study

Patient Questionnaire #2

This is the second of two questionnaires. Before you proceed, please make sure you have completed the first questionnaire (found in a separate envelope).

[Patient alert card is included in envelope 2]

The purpose of the second questionnaire is to learn more about your understanding of important safety information related to Xarelto <u>after</u> reviewing the Xarelto Patient Alert Card.

<u>Before you complete this questionnaire, please read through the attached Xarelto Patient Alert Card as if you just had received it for the first time from your doctor</u>.

After you have read the Xarelto Patient Alert Card, please answer the following questions related to the safety information provided in the card.

Q1. Xarelto is a prescription medicine used to thin the blood to prevent blood clots?

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q2. Blood thinning medications, such as Xarelto, may cause bleeding. Please remember that this question is asking about your knowledge in general and not about your own experience.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q3. Which of the following are possible signs or symptoms of bleeding while taking Xarelto? Please remember that this question is asking about your knowledge in general and <u>not</u> about your own experience.

Check the box Yes, No, or I don't know for each of the following items.

	Yes, this **<u>may be</u>** a sign or symptom of bleeding when taking Xarelto	**No,** this is **<u>not</u>** a sign or symptom of bleeding when taking Xarelto	**<u>I don't know</u>** if this is a sign or symptom of bleeding when taking Xarelto
Pain	☐	☐	☐
Swelling or discomfort	☐	☐	☐
Headache, dizziness, or weakness	☐	☐	☐
Unusual bruising	☐	☐	☐

Q4. I must <u>not</u> stop taking Xarelto at any time without consulting with my doctor.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q5. I need to speak to my doctor prior to any intake of other medication(s).

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q6. I need to inform my doctor or dentist about Xarelto intake prior to any kind of surgery or invasive procedure.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q7. I need to tell my doctor right away if I have any signs or symptoms of bleeding while taking Xarelto.

- ☐ Yes, this is true
- ☐ No, this is not true
- ☐ I don't know

Q8. Should Xarelto (15 mg and 20 mg tablets) be taken with food?

- ☐ Yes
- ☐ No
- ☐ I don't know

Q9. What should you do to ensure Xarelto is effective in preventing blood clots?

Select <u>all</u> that apply.

- ☐ Take Xarelto exactly as prescribed by your Health Care Professional
- ☐ Take Xarelto only when you do not feel well
- ☐ Do not miss a dose of Xarelto
- ☐ I don't know

The next section is about the Xarelto Patient Alert Card that you reviewed before completing the second questionnaire. The Xarelto Patient Alert Card contains important safety information about Xarelto.

Q10. <u>Prior to today</u>, had you <u>received or been given</u> the Patient Alert Card for Xarelto?

- ☐ Yes → **<u>Go to Q11</u>**
- ☐ No → **<u>Go to Q15</u>**
- ☐ I don't remember → **<u>Go to Q15</u>**

Answer questions Q11 – Q14 only if you received a Patient Alert Card for Xarelto.

Q11. <u>Prior to today</u>, had you ever <u>read</u> the Patient Alert Card for Xarelto?

- ☐ Yes → **<u>Go to Q13</u>**
- ☐ No → **<u>Go to Q12</u>**
- ☐ I don't remember → **<u>Go to Q13</u>**

Q12. Is there a reason why you have not read the Patient Alert Card for Xarelto, prior to today?

Select <u>all</u> that apply.

- ☐ I haven't taken the medication yet
- ☐ Someone else explained it to me
- ☐ I lost the patient alert card
- ☐ I already knew the information
- ☐ I have not had the time yet
- ☐ I am not interested in reading it
- ☐ Other

Q13. How much of the time do you keep the Xarelto Patient Alert Card with you?

Select the <u>one</u> answer that best applies to you

- ☐ All the time
- ☐ Some of the time
- ☐ None of the time
- ☐ I don't know

Q14. Who do you show the Patient Alert Card to?

Select the <u>one</u> answer that best applies to you

- ☐ Every doctor or dentist that I visit
- ☐ No one, it is just for my information
- ☐ Only to healthcare professionals who ask for it
- ☐ I don't know

Q15. <u>Prior to today</u>, had someone explained the information in the Patient Alert Card for Xarelto to you?

Select <u>all</u> that apply.

- ☐ Yes, a doctor
- ☐ Yes, a nurse
- ☐ Yes, a pharmacist or someone at the chemists
- ☐ Yes, a friend, family member, or carer
- ☐ No
- ☐ I don't know

You have now reached the end of the second questionnaire. Thank you again for taking time to take part in this study!

If you have any questions about how to safely take Xarelto or about the potential side effects associated with Xarelto, you should talk with your healthcare professional.

Please place your completed questionnaire back into the envelope and seal the envelope. Then, notify the study coordinator that you are finished.

Bayer HealthCare

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

Study Number: 16167

Drug: Xarelto (Rivaroxaban)

Date: 9 October 2014

On top of established Bayer standard operating procedures, i. e. delegation of the protocol review to the Protocol Review Committee, this is to document QPPV involvement in the review and sign-off of the study protocol for the specific study no. 16167 with the title "Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages" conducted in the EU".

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