XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Summary of Risk Management Plan for Xarelto (rivaroxaban)

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

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

This summary of the RMP for Xarelto should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xarelto's RMP.

1. The Medicine and what it is used for

Xarelto is authorised for:

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

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

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

2. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

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

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

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

Together, these measures constitute *routine risk minimisation* measures.

In the case of Xarelto, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

2.1 List of Important Risks and Missing Information

Important risks of Xarelto are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xarelto. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity • Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension
Missing information	• Patients with severe renal impairment (CrCl < 30 mL/min) • Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir) • Remedial pro-coagulant therapy for excessive haemorrhage • Pregnant or breast-feeding women • Patients with atrial fibrillation (AF) and a prosthetic heart valve • Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

2.2 Summary of Important Risks

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

Important identified risk: haemorrhage	
Evidence for linking the risk to the medicine	The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Evidence was mainly taken from pivotal studies, EU RMPs and PBRERs/PSURs.
Risk factors and risk groups	Patients with certain pre-existing conditions (e.g. active cancer, previous stroke, bronchiectasis, history of bleeding, anaemia, uncontrolled hypertension, renal impairment, known GI ulcerations), those receiving concurrent antithrombotics, or the elderly, may be at higher risk of bleeding. Post-operative patients are generally at high risk of bleeding, especially during treatment with anticoagulants. Pre-menopausal women may be at risk for menorrhagia.
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications): Section 4.4 (Special warnings and precautions for use): Section 4.8 (Undesirable effects) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Important potential risk: embryo-fetal toxicity	
Evidence for linking the risk to the medicine	Pregnant women were excluded from clinical trials and rivaroxaban is contraindicated in pregnancy according to the SmPC, due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta. Therefore, the overall experience is limited.
Risk factors and risk groups	The majority of patients receiving rivaroxaban are elderly patients. Only in patients with ACS, and those undergoing treatment for VTE, there may be a higher possibility of women with child-bearing potential receiving rivaroxaban. A large population-based study concluded that a history of DVT is an independent risk factor for spontaneous preterm delivery (33). This study compared all pregnancies of patients with and without a history of DVT: there were 212,086 deliveries, of which 122 (0.06%) occurred in patients with a history of DVT. No significant differences were noted between the groups regarding perinatal outcomes such as low Apgar scores, congenital malformations or perinatal mortality. Ben-Joseph et al. determined that patients with a history of DVT were more likely to have caesarean deliveries (OR, 2.6; 95% CI, 1.8–3.8; $p < 0.001$) than non-DVT patients, and DVT was an independent risk factor for preterm birth (OR, 1.8; 95% CI, 1.1–2.9; $p = 0.033$) (33). In a study of 395 patients with a history of VTE and 313 control women stillbirth was slightly more frequent in patients (4.3%) than in controls (3.2%); the difference was not statistically significant. Miscarriage was equally frequent between groups (34). A population-based study in the USA showed that pregnant women with AF (n = 157) were more likely to have babies that needed to be admitted to the neonatal intensive care unit (NICU) than pregnant women without AF (n = 264 573) (NICU admissions: 10.8% vs 5.1%; $p = 0.003$) (35).
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data): Prescription-only medicine Limited pack sizes

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Important potential risk: Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	
Evidence for linking the risk to the medicine	For children too young or unable to swallow rivaroxaban tablets, the drug will be administered orally as a suspension. The drug-device combination product including the pharmaceutical form 1 mg/mL granules for oral suspension needs to be prepared by the child's caregiver using the drug-device combination kit. Errors in the preparation of the suspension, as well as its subsequent application, may result in over- or underdosing. Overdose The increased risk for bleeding under treatment with an anticoagulant compound is contributable to its pharmacodynamic property in preventing blood from clotting (pharmacological mode of action is dose dependent inhibition of factor Xa). Evidence was mainly taken from pivotal studies, EU RMPs and PBRERs/PSURs. Underdose Lack of drug effect; recurrence of VTE
Risk factors and risk groups	Children diagnosed with VTE and too young or unable to swallow rivaroxaban tablets who are treated with the liquid formulation granules for oral suspension.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC (Xarelto 1 mg/mL granules for oral suspension) Section 4.2 (Posology and method of administration) Section 4.4 (Special warnings and precautions for use) Section 6.5 (Nature and contents of container) Section 6.6 (Special precautions for disposal and other handling) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** Educational material for prescribers Patient alert cards Video

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Missing information: Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)	
Evidence for linking the risk to the medicine	Pharmacokinetc data
Risk factors and risk groups	Respective patients
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medicinal products and other forms of interaction) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

Missing information: Pregnant or breast-feeding women	
Evidence for linking the risk to the medicine	Pharmacokinetic data, pregnancy/nursing mother reports
Risk factors and risk groups	Respective population
Risk minimisation measures	**Routine risk minimisation measures:** SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data) Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Drug utilisation and specific outcome studies Modified Prescription Event Monitoring Study (M-PEM) Specialist Cohort Event Monitoring Studies (SCEM ROSE and SCEM ACS)

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

2.3 Post-authorisation Development Plan

2.3.1 Studies which are conditions of the Marketing Authorisation

THIN (UK) (SN 16647)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

GePaRD (Germany) (SN 16159)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

PHARMO (the Netherlands) (SN 16646)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Swedish National Registers (Sweden) (SN 17543)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

M-PEM (SN 16164)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

SCEM ACS (SN 17542)

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

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

2.3.2 Other Studies in Post-authorisation Development Plan

Risk Minimisation Survey Study (SN 16167)

Purpose of the study: This study serves to evaluate the effectiveness of the additional risk minimisation tools developed for rivaroxaban, which include a Prescriber's Guide (PG) and Patient Alert Card (PAC), with the aim of increasing awareness and understanding among physicians and patients about the potential bleeding risk during treatment with rivaroxaban. The primary objectives of the study are to measure whether physicians and patients received and used the prescriber guide and PAC, respectively, and to evaluate their awareness and understanding of the key safety messages. Evaluation surveys were planned for administration in 3 waves at 18 months, 3 years, and 7 years post launch. The patient surveys have been discontinued after wave 1. This study is being conducted by RTI Health Solutions, with assistance of Kantar Health for field operations.

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

Paediatric Investigational Programme (PIP)

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

Category 3 - Required additional pharmacovigilance activities

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

XARELTO®
(Rivaroxaban)
EU Risk Management Plan

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

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

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

Study Status	Summary of objectives	Safety concerns/efficacy issue addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Non-interventional, multicentre cohort study In planning	To investigate the safety and tolerability of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE patients and in children with VTE treated with other anticoagulants.	**Important identified risk:** • Haemorrhage **Important potential risk:** • Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension	Feasibility report	Submission Q1 2021
			Start of data collection	Q3-Q4 2021 (estimated)
			Interim report (study progress report)	One year after start of data collection Q3-Q4 2022 (estimated)
			End of data collection	Q3-Q4 2024 (estimated)
			Final report of study results (6 months after end of data collection LP treated with Xarelto)	Q1-Q2 2025 (estimated)