EU RISK MANAGEMENT PLAN

FOR

RIVAROXABAN 2.5 MG, 10 MG, 15 MG, AND 20 MG ORODISPERSIBLE FILMS

RMP version to be assessed as part of this application

RMP Version number: 0.2

Data lock point for this RMP: 21/01/2025

Date of final sign off: 05/03/2025

Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application

Summary of significant changes in this RMP: Not applicable, this is the first RMP for Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films for initial marketing authorisation

Other RMP versions under evaluation: Not applicable

RMP version number	Submitted on	Submitted within procedure number
Not applicable	Not applicable	Not applicable

Details of the currently approved RMP:

RMP version number	Approved with procedure	Date of approval (opinion date)
Not applicable	Not applicable	Not applicable

QPPV name: Mr. Jose Alberto Ayala Ortiz

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorization holder’s QPPV. The electronic signature is available on file.

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List of Abbreviations

AF	:	Atrial Fibrillation
ACS	:	Acute Coronary Syndrome
ATC	:	Anatomical Therapeutic Chemical
ASA	:	Acetylsalicylic Acid
CAD	:	Coronary Artery Disease
DVT	:	Deep Vein Thrombosis
EEA	:	European Economic Area
EU	:	European Union
MA	:	Marketing Authorisation
MAH	:	Marketing Authorization Holder
MS	:	Member State
PAD	:	Peripheral Artery Disease
PE	:	Pulmonary Embolism
PI	:	Product Information
PL	:	Package Leaflet
POM	:	Prescription Only Medicine
PSUR	:	Periodic Safety Update Report
QPPV	:	Qualified Person for Pharmacovigilance
RMP	:	Risk Management Plan
SmPC	:	Summary of Product Characteristics
VTE	:	Venous Thromboembolism

Part I: Product(s) Overview

The Risk Management Plan (RMP) is prepared in line with the current "Guideline on good Pharmacovigilance practices (GVP) Module V - Risk Management Systems and the Guidance on format of the Risk Management Plan (RMP) in the EU.

Table Part I.1 – Product Overview

Active substance(s)	Rivaroxaban
Pharmacotherapeutic group(s) (ATC Code)	B01AF01
Applicant	Koanaa Healthcare Spain, S.L.
Medicinal products to which this RMP refers	04
Invented name(s) in the European Economic Area (EEA)	Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	Chemical class: Rivaroxaban is an antithrombotic agent, direct factor Xa Inhibitor. The chemical name is 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1 ,3-oxazolidin-5-yl} methyl)-thiophenecarboxamide
	Summary of mode of action: Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.
	Important information about its composition: none
Hyperlink to the Product Information	Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films
Indication(s) in the EEA	**Current:** <u>Rivaroxaban 2.5 mg</u> orodispersible films by Koanaa: • 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. • co-administered with 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. Rivaroxaban 10 mg orodispersible films by Koanaa is indicated for: • the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery. • the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Rivaroxaban 15 mg and 20 mg orodispersible films by Koanaa are indicated for: • the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. • the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. Rivaroxaban 15 mg orodispersible films by Koanaa is indicated for the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment. Rivaroxaban 20 mg orodispersible films by Koanaa is indicated for the treatment of VTE and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.
	Proposed: Not applicable
Dosage in the EEA	**Current:** Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery The recommended dose is 10 mg rivaroxaban once daily. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and

	prevention of recurrent DVT and PE. When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban 10 mg once daily, a dose of 20 mg once daily should be considered. Prevention of stroke and Systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack The recommended dose is 20 mg once daily, which is also the recommended maximum dose. Prevention of atherothrombotic events in adult patients after ACS with elevated cardiac biomarkers The recommended dose is 2.5 mg twice daily. Prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events. The recommended dose is 2.5 mg twice daily. Treatment of VTE and prevention of VTE recurrence in children and adolescents - Body weight from 30 to 50 kg: a once daily dose of 15 mg Rivaroxaban is recommended. This is the maximum daily dose. - Body weight of 50 kg or more: a once daily dose of 20 mg Rivaroxaban is recommended. This is the maximum daily dose. - Rivaroxaban Koanaa films should not be prescribed for patients with body weight less than 30 kg.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Orodispersible films 2.5 mg, 10 mg, 15 mg and 20 mg
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

The Marketing Authorisation (MA) application for rivaroxaban 2.5 mg, 10 mg and 15 mg and 20 mg orodispersible films is being submitted as Generic Application under article 10(1) of Directive 2001/83/EC and Directive 2010/84/EU.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Not Applicable

Part II: Module SII - Non-clinical part of the safety specification

Not Applicable

Part II: Module SIII - Clinical trial exposure

Not Applicable

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

Not applicable

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Summary of safety concerns for Rivaroxaban are presented in the table below:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important Identified Risk	Haemorrhage
Important Potential Risk	Embryo-fetal toxicity
Missing information	Remedial pro-coagulant therapy for excessive haemorrhage
	Patients with atrial fibrillation (AF) and prosthetic heart valve

The above stated list of safety concerns is obtained from the approved EU Safety RMP of Xarelto® (Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets), version 14.3 dated 24-Aug-2023 (Bayer) published by European Medicines Agency (EMA) [1]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

The safety concerns of rivaroxaban are considered to be well established. Routine pharmacovigilance activities are deemed sufficient.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

III 1.1 Specific adverse reaction follow-up questionnaires for safety concerns:

Additionally, as a part of routine pharmacovigilance targeted follow-up questionnaires are planned to obtain further clinical details to aid causality assessment for the following safety concerns:

1. Liver-Related Adverse Events
2. Renal Impairment/Renal Failure

The specific questionnaires are planned for collecting further relevant information about each of the suspected adverse reactions.

The forms and mock-ups are provided in **Annex 4** of the RMP.

III 1.2 Other forms of routine pharmacovigilance activities for safety concerns:

None

III.2 Additional pharmacovigilance activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended for rivaroxaban.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for post-authorisation efficacy studies

There are no plans for post-authorisation efficacy studies

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk: Haemorrhage	Routine risk communication: Summary of product characteristics (SmPC): Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.5 (Interaction with other medical products and other forms of interactions) Section 4.8 (Undesirable effects) Section 4.9 (Overdose) & subsections (Management of bleeding). Indication specific differences are listed in the respective SmPCs. Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.4 (Special warnings and precautions for use), and subsections: Information on patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors is provided -monitoring for signs of bleeding complications. Information on groups of patients with an increased bleeding risk is provided. Information for surgery and interventions is provided - information on drug discontinuation. Information on patients with neuraxial (epidural/spinal) anaesthesia is provided - information on monitoring of epidural or spinal hematoma Section 4.5 (Interaction with other medicinal products and other forms of interaction): Information on pharmacokinetic interactions and pharmacodynamic interactions, food and dairy products Section 4.9 (Overdose):

	Information on the management of overdose and bleeding complications is communicated. Other routine risk minimisation measures beyond the Product Information: Pack size limited. Legal status: Prescription Only Medicine (POM)

Safety concern	**Routine risk minimisation activities**
Important Potential Risk: Embryo-fetal toxicity	Routine risk communication: SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data) Routine risk minimisation activities recommending specific clinical measures to address the risk: Section 4.6 (Pregnancy and lactation) Information: Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy. Other routine risk minimisation measures beyond the Product Information: None

Safety concern	**Routine risk minimisation activities**
Missing information: Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk communication: SmPCs: Section 4.9 (Overdose) Routine risk minimisation activities recommending specific clinical measures to address the risk: Additional information for management of bleeding. Other routine risk minimisation measures beyond the Product Information: Legal status: POM Limited pack sizes
Missing information: Patients with atrial	Routine risk communication:

fibrillation (AF) and prosthetic heart valve	SmPCs: Section 4.4 (Special warnings and precautions for use) Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: POM Limited pack sizes

V.2. Additional Risk Minimisation Measures

This medicine has as additional risk minimisation measures educational material for prescribers and patient alert card to increase awareness about the risk of bleeding during the treatment with rivaroxaban.

In each Member State (MS) where rivaroxaban is marketed, the MAH shall provide updated additional educational material for prescribers and patient alert cards.

Additional Risk Minimisation Measures: Educational material for prescribers and patient alert card

Objectives:

The aim of the introduction of additional educational materials is to increase the awareness and reduction of the bleeding risk during treatment with rivaroxaban.

The objectives of the label text are to prevent physicians from prescribing rivaroxaban to certain patient groups at high risk of bleeding, and to ensure that use of rivaroxaban in other patients with conditions or receiving treatments that can increase the risk of bleeding will be carefully monitored to minimise the risk of bleeding complications.

Rationale for the additional risk minimisation activity:

The applicant proposes to provide the following additional risk minimisation material to increase the understanding of the safe and effective use of rivaroxaban, and to counsel patients who are either currently receiving rivaroxaban or in whom rivaroxaban treatment is planned.

All healthcare professionals who are expected to use rivaroxaban are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Prescriber guide
- Patient alert card

The Prescriber guide is complemented with the SmPC which helps to remind physicians about the need to monitor and perform testing on patients before and/or periodically after treatment for early detection of haemorrhage.

The patient alert card will be supplied as wallet-sized, to enable patients to readily carry them.

Target audience and planned distribution path:

Prescribing physicians and patients receiving rivaroxaban are provided with the educational material as agreed in the individual country with the national competent authority (NCA) in each MS prior to rivaroxaban launch.

Also, the prescriber guide and patient alert card will be shared by Koanaa healthcare medical information team to HCPs/ Physician who can request the material to Koanaa healthcare email pharmacovigilance@koanaa.com or pharmacovigilance@shilpamedicare.com

Plans to evaluate the effectiveness of the interventions and criteria for success:

Plans to evaluate the effectiveness of the interventions:

Quantitative and qualitative medical assessment of haemorrhage cases received would be performed and observed periodically.

Periodic analysis and haemorrhage risk details update in every periodic safety update report (PSUR).

Criteria for success:

Reduction in the frequency and/or severity of haemorrhage related adverse drug reactions in relation to patients' exposure to rivaroxaban.

The proposed educational material and the key elements to be included in the rivaroxaban risk minimization materials are appended as Annex 6 of this RMP.

Removal of additional risk minimisation activities

None

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Haemorrhage	Routine Risk Minimisation Measures: SmPCs: Section 4.3 (Contraindications) Section 4.4 (Special warnings and precautions for use) Section 4.8 (Undesirable effects) Prescription only medicine Limited pack sizes Additional Risk Minimisation Measures: - Educational material for prescribers	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional Pharmacovigilance Activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- Patient alert card	
Important Potential Risks		
Embryo-fetal toxicity	Routine Risk Minimisation Measures: SmPCs: Section 4.3 (Contraindications) Section 4.6 (Fertility, pregnancy and breast-feeding) Section 5.3 (Preclinical safety data). Prescription only medicine Limited pack sizes Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None
Missing information		
Remedial pro-coagulant therapy for excessive haemorrhage	Routine Risk Minimisation Measures: SmPCs: Section 4.9 (Overdose) Prescription only medicine Limited pack sizes Additional Risk Minimisation Measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Patients with atrial fibrillation (AF) and prosthetic heart valve	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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Rivaroxaban 2.5 mg, 10 mg and 15 mg, 20 mg orodispersible films (rivaroxaban).

This is a summary of the risk management plan (RMP) for rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films. The RMP details important risks of rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films, how these risks can be minimised.

Rivaroxaban Summary of Product Characteristics (SmPC) and its Package Leaflet (PIL) give essential information to healthcare professionals and patients on how rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films should be used.

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

I. The medicine and what it is used for

Rivaroxaban 2.5 mg orodispersible films by Koanaa is authorised:

- co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.
- co-administered with ASA, 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.

Rivaroxaban 10 mg orodispersible films by Koanaa is authorised for:

- the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.
- the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Rivaroxaban 15 mg and 20 mg orodispersible films by Koanaa are authorised for:

- the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
- the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.
- the treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

It contains rivaroxaban as the active substance, and it is taken orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of rivaroxaban 2.5 mg, 10 mg, 15mg and 20mg orodispersible films, together with measures to minimise such risks and the proposed studies for learning more about rivaroxaban'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 rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films, these measures are supplemented with additional risk minimisation measures mentioned under relevant sections of important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (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 rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films is not yet available, it is listed under "missing information".

II.A List of important risks and missing information

Important risks of Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 rivaroxaban 2.5 mg, 10 mg, 15 mg and 20mg orodispersible films. 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).

List of important risks and missing information	
Important Identified Risk	Haemorrhage
Important Potential Risk	Embryo-fetal toxicity
Missing information	Remedial pro-coagulant therapy for excessive haemorrhage
	Patients with atrial fibrillation (AF) and prosthetic heart valve

II.B Summary of important risks

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).
Risk factors and risk groups	Patients with certain pre-existing conditions (e.g. active

Important Identified Risk: Haemorrhage	
	cancer, previous stroke, bronchiectasis, history of bleeding, anaemia, uncontrolled hypertension, renal impairment, known Gastrointestinal 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 (hypermenorrhoea).
Risk minimisation measures	<u>Routine Risk Minimisation Measures:</u> 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 <u>Additional Risk Minimisation Measures:</u> - Educational material for prescribers - Patient alert card
Additional pharmacovigilance activities	None

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 [1].
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 [1]. A large population-based study concluded that a history of DVT is an independent risk factor for spontaneous preterm delivery. 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.

Important Potential Risk: Embryo-fetal toxicity	
	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). In a study of 395 patients with a history of VTE and 313 control women still-birth 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. A population-based study in the USA showed that pregnant women with AF (n = 1 57) 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) [1]
Risk minimisation measures	<u>Routine Risk Minimisation Measures:</u> 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 <u>Additional Risk Minimisation Measures:</u> None
Additional pharmacovigilance activities	None

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	Patients with excessive haemorrhage who requires remedial pro-coagulant therapy.
Risk minimisation measures	<u>Routine Risk Minimisation Measures:</u> SmPCs: Section 4.9 (Overdose) Prescription only medicine Limited pack sizes <u>Additional Risk Minimisation Measures:</u>

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

Missing Information: Patients with atrial fibrillation (AF) and prosthetic heart valve	
Evidence for linking the risk to the medicine	Patients with prosthetic heart valves not studied
Risk factors and risk groups	Patients with AF and prosthetic heart valve who requires anticoagulatory therapy.
Risk minimisation measures	<u>Routine Risk Minimisation Measures:</u> SmPCs: Section 4.4 (Special warnings and precautions for use) Prescription only medicine Limited pack sizes <u>Additional Risk Minimisation Measures:</u> None
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg orodispersible films.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

Not applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

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Rivaroxaban Follow-up

Liver-related Adverse Events

Annex 4.1 - Questionnaire Liver-Related Adverse Events

SECTION I - REFERENCE ID			
KOANAA CASE ID:	🔒	**STUDY/ PROJECT ID:**	**PATIENT ID:**
SECTION II - REPORTER/PATIENT INFORMATION			
REPORTER: ☐ Physician ☐ Nurse ☐ Patient ☐ Other (specify):			
REPORTER CONTACT INFORMATION			
Name:		**Institution/Practice Name:**	
Address:			
ZIP Code:	**City:**	**Country:**	
Phone:	**Fax:**	**Email:**	
PATIENT INFORMATION			
Age (years): (*at onset of event)*	Gender: ☐ Male ☐ Female	Weight (kg):	Height (cm):
Race: White ☐ Black or African American ☐ American Indian/Alaska Native ☐ Native Hawaiian/Pacific Islander ☐ Asian ☐ Other (specify):			
Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown			
SECTION III - PRODUCT INFORMATION (Rivaroxaban)			
INDICATION			
☐ VTE prevention in Major orthopedic surgery ☐ Total hip replacement ☐ Total knee replacement ☐ Other lower limbs *(specify}:*			
☐ Stroke prevention in atrial fibrillation	☐ VTE treatment (and secondary prevention)		
☐ Other *(specify):*	☐ Unknown		
Therapy started: (hours) after major orthopedic surgery		**Dose / Frequency:**	
SECTION IV -ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Outcome *(if fatal, see SECTION VII):*
TREATMENT PROVIDED FOR LIVER EVENT			

☐ Yes *(specify):*	☐ No treatment ☐ Unknown

SUSPECTED CAUSE OF EVENT

Related to Rivaroxaban treatment?

☐ Yes ☐ No *(specify alternative explanation/other contributing factors):*

Action taken with Rivaroxaban	**Date (dd/mm/yyyy)**		
☐ Dose increased	☐ Dose reduced		New dose:
☐ Interrupted		From:	To:
☐ Withdrawn			
☐ None	☐ Unknown		

SECTION IV A-RELEVANT CLINICAL SYMPTOMS (to AE of interest, which were not reported at time of first report)

Signs and symptoms	**Details** *(e.g. provide values or frequency if available)*
☐ Asthenia / Fatigue	
☐ Pruritus (itching)	
☐ Jaundice	
☐ Ascites	
☐ Altered level of consciousness (encephalopathy) ☐ Confusion ☐ Coma	
☐ Hepatomegaly	
☐ Splenomegaly	
☐ Dark Urine	
☐ Spider nevi	
☐ Other liver-related symptoms and signs (specify):	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS

Laboratory Data	**Units/ Reference Range**	**Before start of drug**	**While taking the drug**			**Normalized after end of drug?**
		Date (dd/mm/yyyy)	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**

Alk. phosphatase						☐
Total bilirubin						☐
Conjugated (direct) bilirubin						☐
ALT/ SGPT						☐
AST/ SGOT						☐
Gamma GT						☐
PT						☐
INR						☐
Albumin						☐
LDH						☐
HBDH						☐
Complete blood count Hemoglobin						☐
Eosinophils						☐
Amylase						☐
Lipase						☐
Creatinine kinase						☐
Choline esterase						☐
Other *(specify):*						☐

Serology test for virus infection	**Test date** *(dd/mm/yyyy)*	**Results with units**	**Comments**
☐ Anti-Hep. A Virus IgM Antibodies			
☐ Hepatitis B surface Antigen ☐ Hepatitis B PCR (viral copies) ☐ Anti-Hep. B surface Antibodies ☐ Anti-Hep. B core IgM Antibodies ☐ Anti-Hep.s B core IgG Antibodies			
☐ Anti-Hepatitis C Virus Antibodies ☐ Anti-Hep. C Virus IgM Antibodies ☐ Hepatitis C PCR (viral copies)			
☐ Anti-Hep. D Virus IgM Antibodies ☐ Hepatitis D PCR (viral copies)			
☐ Anti-Hep. E virus IgG Antibodies ☐ Anti-Hep. E virus IgM Antibodies ☐ Hepatitis E virus RNA (PCR)			
☐ Anti-Cytomegalovirus (CMV) IgM			

Antibodies ☐ Cytomegalovirus (CMV) PCR			
☐ Anti-Epstein-Barr Virus (EBV) IgM Antibodies ☐ EBV other (specify):			
☐ Adenovirus IgG ☐ Adenovirus IgM			
☐ Coxsackie IgG ☐ Coxsackie IgM			
☐ Herpes Simplex IgG ☐ Herpes Simplex IgM			
☐ Toxoplasmosis			
☐ Brucella *(specify):*			
☐ Leptospira *(specify):*			
☐ Other Serology test *(specify):*			

Autoimmune markers	**Test date** *(dd/mm/yyyy)*	**Results with units**	**Comments**
☐ Antinuclear Ab (ANA)			
☐ Anti-smooth muscle Ab (SMA)			
☐ Anti-mitochondrial Antibodies			
☐ Anti-KLM1 Antibodies			
☐ Anti-SLA / LP			
☐ Atypical p-ANCA			
☐ Other autoimmune test *(specify):*			

Further investigations	**Test date** ***(dd/mm/yyyy)***	**Short summary of the result**
☐ Ultrasound		
☐ CT		
☐ MRI		
☐ ERCP		
☐ Liver biopsy		
☐ Other *(specify):*		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered *hepatotoxic medications* including any drugs given up to *2 months prior to* the liver event.

Concomitant product name	Route	Indication for use	Dose/ Frequency	Start date *(dd/mm/yyyy)*	Stop date *(dd/mm/yyyy)*	Possible cause for the event?
☐ Other antithrombotic therapy						☐
☐ Paracetamol						☐
☐ Methotrexate						☐
☐ Amiodarone						☐
☐ NSAIDs *(specify):*						☐
☐ Herbal substances *(specify):*						☐
☐ Antibiotics *(specify):*						☐
☐ Cancer therapy *(specify):*						☐
☐ Halothane						☐
☐ Other *(specify):*						☐

SECTION VI - MEDICAL HISTORY/ RISK FACTORS

Relevant medical history/ Concomitant conditions	Start date *(dd/mm/yyyy)*	Ongoing	Stop date *(dd/mm/yyyy)*	Details
☐ Active malignancy				*Specify type:*
☐ Liver cancer/ metastases				
☐ Liver cirrhosis/ fibrosis ☐ Child-Pugh Class:				
☐ Fatty liver				
☐ Viral Hepatitis				*Specify acute or chronic, type.*
☐ Hepatis vaccination		N/A	N/A	*Specify type:*
☐ Biliary disease				

☐ Pancreatitis				
☐ Autoimmune disease *(specify):*				
☐ Hemochromatosis				
☐ Wilson's disease				
☐ Alpha 1-antitrypsin deficiency				
☐ Diabetes mellitus				
☐ Heart failure				
☐ Renal failure				
☐ Alcohol misuse				
☐ Surgery		N/A	N/A	*Specify type of surgery and type of anesthesia:*
☐ Other *(specify):*		☐		

SECTION VII -ADDITIONAL INFORMATION/ COMMENTS *(if any):*

This section con also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death ***(If selected outcome was fatal)***	**Date of death** ***(dd/mm/yyyy)***	**Autopsy**	**Autopsy details** ***Continue with SECTION IV***
		☐	

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Rivaroxaban Questionnaire for Liver-related Adverse Events, V 0.1, 26-Aug-2024

Rivaroxaban Follow-up

Renal Failure

Annex 4.2 - Questionnaire Renal Failure

SECTION I - REFERENCE ID			
KOANAA CASE ID:		**STUDY/ PROJECT ID:**	**PATIENT ID:**

SECTION II - REPORTER/PATIENT INFORMATION			
REPORTER: ☐ Physician ☐ Nurse ☐ Patient ☐ Other (specify):			
REPORTER CONTACT INFORMATION			
Name:		**Institution/Practice Name:**	
Address:			
ZIP Code:	**City:**	**Country:**	
Phone:	**Fax:**	**Email:**	

PATIENT INFORMATION			
Age (years): *(at onset of event)*	Gender: ☐ Male ☐ Female	Weight (kg):	Height (cm):
Race: ☐ White ☐ Black or African American ☐ American Indian/ Alaska Native ☐ Native Hawaiian/Pacific Islander ☐ Asian ☐ Other (specify}:			
Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown			

SECTION III - PRODUCT INFORMATION (Rivaroxaban)	
INDICATION	
☐ VTE prevention in Major orthopedic surgery ☐ Total hip replacement ☐ Total knee replacement ☐ Other lower limbs *(specify}:*	
☐ Stroke prevention in atrial fibrillation	☐ VTE treatment (and secondary prevention)
☐ Other (specify):	☐ Unknown
Therapy started: (days) after major orthopedic surgery	Dose / Frequency:

SECTION IV -ADVERSE EVENT INFORMATION			
Event *(term that triggered follow-up)*	**Start date**	**Stop date *(dd/mm/yy***	**Outcome *(if fatal, see SECTION VII):***

	(dd/mm/yyyy)	***yy)***	
TREATMENT PROVIDED FOR RENAL EVENT			
Yes *(specify):*		☐ **No treatment** ☐ **Unknown**	
SUSPECTED CAUSE OF EVENT			
Related to Rivaroxaban treatment? ☐ Yes ☐ NO *(specify alternative explanation/other contributing factors):*			
Action taken with Rivaroxaban		**Date (dd/mm/yyyy)**	
☐ **Dose increased**	☐ **Dose reduced**		**New dose:**
☐ **Interrupted**		**From:**	**To:**
☐ **Withdrawn**			
☐ **None**	☐ **Unknown**		

SECTION IV A-RELEVANT CLINICAL SYMPTOMS (to AE of interest, which were not reported at time of first report)	
Signs or symptoms	**Details** *(e.g. provide values or frequency if available)*
☐ Oliguria	
☐ Hematuria	
☐ Fever	
☐ Anuria	
☐ Dysuria	
☐ Polyuria	
☐ Back pain	
☐ Hypertension	
☐ Other *(specify):*	

SECTION IV B - RELEVANT LABORATORY DATA OR RESULTS OF OTHER DIAGNOSTIC INVESTIGATIONS						
Laboratory Data	**Units/ Reference Range**	**Before start of drug**	**While taking the drug**			**Normalized after end of drug?**
		Date (dd/mm/yyyy)	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**	**Date (dd/mm/yyyy)**
Blood test						

Serum creatinine (Scr)						☐
Creatinine kinase (CK)						☐
GFR						☐
Urea						☐
Potassium (K)						☐
Sodium (Na)						☐
Phosphate						☐
Calcium						☐
Albumin						☐
CRP						☐
Leukocytes						☐
LDH						☐
HBDH						☐
Blood Gas Analysis						
pH						☐
Bicarbonate						☐
Oxygen						☐
Urinalysis/ Sediment						
Proteinuria						☐
Hematuria						☐
Leukocyturia						☐
Dysmorphic erythrocytes						☐
Casts						☐
Other (e.g. antibodies, urinary or serum eosinophils, specify):						☐

						☐
						☐

Further investigations	**Test date** ***(dd/mm/yyyy)***	**Short summary of the result**
☐ Ultrasound		
☐ CT		
☐ MRI		
☐ Renal biopsy		
☐ Other *(specify):*		

SECTION V - RELEVANT CONCOMITANT MEDICATION

Concomitantly administered drugs with known renal side effects given up to 2 months prior to the reported event.

Concomitant product name	**Route**	**Indication for use**	**Dose/ Frequency**	**Start date** ***(dd/mm/yyyy)***	**Stop date** ***(dd/mm/yyyy)***	**Possible cause for the event?**
Other antithrombotic therapy						☐
NSAIDs (specify):						☐
ACE inhibitors *(specify):*						☐
Contrast agents *(specify):*						☐
Antibiotics *(specify):*						☐
Cancer therapy *(specify):*						☐
Herbal substances *(specify):*						☐
						☐
						☐
						☐

SECTION VI - MEDICAL HISTORY/ RISK FACTORS

Relevant medical history/ Concomitant conditions	**Start date** ***(dd/mm/yyyy)***	**Ongoing**	**Stop date** ***(dd/mm/yyyy)***	**Details**
☐ Active malignancy		☐		Specify type:

☐ Renal tumor		☐		
☐ Hypertension		☐		
☐ Infection *(specify):*		☐		
☐ Glomerulonephritis		☐		
☐ Interstitial nephritis		☐		
☐ Autoimmune disease *(specify):*		☐		
☐ Diabetes mellitus		☐		
☐ Surgery *(specify type of surgery, type of anesthesia, hypotension during surgery)*		N/A	N/A	
☐ Other *(specify):*		☐		

SECTION VII -ADDITIONAL INFORMATION/ COMMENTS ***(if any):***

This section con also be used to provide information on any of the sections above. Please note the relevant section number below.

Cause of death ***(If selected outcome was fatal)***	**Date of death** ***(dd/mm/yyyy)***	**Autopsy**	**Autopsy details** ***Continue with SECTION IV***

Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.

Rivaroxaban Questionnaire for Renal Failure, V 0.1, 26-Aug-2024

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Rivaroxaban has educational materials for physicians and patients that serve as additional risk minimisation measures to increase awareness about the risk of bleeding during the treatment with rivaroxaban.

The key elements of such materials are provided below.

The educational materials contain the following key elements: Prescriber Guide and patient alert card.

Rivaroxaban Prescriber Guide

This guide is to be used to support the appropriate use of rivaroxaban in the following indications:

- Prevention of stroke and systemic embolism in eligible adults with non-valvular atrial fibrillation (AF)
- Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults (not recommended for use in haemodynamically unstable PE patients)
- Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
- Prevention of atherothrombotic events in adults after an acute coronary syndrome (ACS) with elevated cardiac biomarkers, in combination with anti-platelet therapy
- Prevention of atherothrombotic events in adult patients with coronary artery disease
- (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

It includes the following information:

- Dosing recommendations
- Method of administration
- Recommendations for changes in anticoagulant treatment
- Contraindications
- Risk of bleeding during rivaroxaban treatment (high risk populations)
- Perioperative management- Spinal/epidural anesthesia or puncture
- Overdose and bleeding complications management
- Coagulation tests

The Prescriber Guide provides recommendations for the use of rivaroxaban in order to minimise the risk of bleeding during treatment with rivaroxaban.

The Prescriber Guide does not substitute the rivaroxaban Summary of Product Characteristics (SmPC).

Rivaroxaban Patient Alert Card

A patient alert card must be provided to each patient who is prescribed rivaroxaban 2.5 mg, 10 mg, 15 mg or 20 mg. Itis provided with the product package. The prescriber should explain the implications of anticoagulant treatment to patients, in particular highlighting the need for:

- Treatment compliance
- Taking medication with or without food (for 15 mg and 20 mg only)

- Recognising signs or symptoms of bleeding
- When to seek medical attention

The patient alert card will inform treating physicians and others health care professionals about the patient's anticoagulation treatment and will contain emergency contact information. The prescriber should instruct patients to carry the patient alert card with them all times and present it to every healthcare provider.

Annex *7* - Other supporting data *(*including referenced material)

References

[1] “https://www.ema.europa.eu/en/documents/rmp-summary/xarelto-epar-risk-management-plan_en.pdf”.

Annex 8 – Summary of changes to the risk management plan over time

Not applicable, as this is the first RMP for Rivaroxaban.