RISK MANAGEMENT PLAN
For
Rivaroxaban

RMP Version to be Assessed as Part of this Application:

RMP Version Number	0.4
Data Lock Point for this RMP	25-Mar-2023
Date of Final Sign Off	24-Jun-2024
Rationale for Submitting an Updated RMP	Core RMP is prepared to harmonise the RMPs of all rivaroxaban marketing authorisations for which the Viatris has an approved RMP RMP updated in Part II Modules SVII-SVIII, Part VI and Part VII in line with reference product RMP (Xarelto EU RMP version 13.4 dated 13-Jun-2022, by Bayer)
Summary of Significant Changes in this RMP	Core RMP is prepared to harmonise the RMPs of all rivaroxaban marketing authorisations for which the Viatris has an approved RMP RMP updated in Part II Modules SVII-SVIII, Part VI and Part VII in line with reference product RMP (Xarelto EU RMP version 13.4 dated 13-Jun-2022, by Bayer), by removing the following safety concerns (classified as 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) - 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.

Other RMP Versions Under Evaluation:

RMP Version Number	Not Applicable
Submitted On	Not Applicable
Procedure Number	Not Applicable

Details of the Current RMP:

Version Number	EMEA/H/C/005600: Version 0.3 SK/H/0260/001-005/DC: Version 0.2 Nat MA in PT (22/H/0046/001-005): Version 0.3
Approved with Procedure	EMEA/H/C/005600 SK/H/0260/001-005/DC 22/H/0046/001-005
Date of Approval (Opinion Date)	EMEA/H/C/005600: 12-Nov-2021 SK/H/0260/001-005/DC: 10-Mar-2022 Nat MA in PT (22/H/0046/001-005): 13-Mar-2023

Approver	Dr Eiko Soehlke, MD MPH, EEA QPPV
Signature	
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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical Classification System
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual recognition and Decentralised Procedures – Human
CP	Centralised Procedure
DCP	Decentralised Procedure
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
PAC	Patient Alert Card
PL	Package leaflet
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTC	Patient treatment course
PTD	Patient treatment Days
PTM	Patient treatment Months
PTY	Patient treatment Years
PVA	Pharmacovigilance Agreement
QPPV	Qualified Person for Pharmacovigilance
MedDRA	Medical Dictionary for Regulatory Activities

DLP	Data Lock Point
SPC	Summary of Product Characteristics
TFU	Targeted Follow Up Questionnaire
WHO	World Health Organization

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Rivaroxaban
Pharmacotherapeutic Group(s) (ATC Code)	Antithrombotic Agents, Direct factor Xa inhibitors, ATC code: B01AF01
Marketing Authorisation holder	Centralized: EMEA/H/C/005600: Viatris Ltd. Decentralized: SK/H/0260/001-004: Viatris Ltd. National Procedure in Portugal: 22/H/0046/001-005: Laboratorios Anova – Produtos Farmacêuticos Lda
Medicinal Products to Which this RMP Refers	4
Invented Name(s) in the European Economic Area (EEA)	Centralized: EMEA/H/C/005600 Rivaroxaban Viatris 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets and Rivaroxaban Viatris 15 mg and 20 mg film-coated tablets (treatment initiation pack) Decentralized:SK/H/0260/001-005 Vixargio 2.5 mg, 10 mg, 15 mg, 20 mg film-coated tablets and Vixargio 15 mg and 20 mg film-coated tablets (treatment initiation pack) National Procedure in Portugal: 22/H/0046/001-005 Rivaroxabano Anova
Marketing Authorisation Procedure	Centralized: EMEA/H/C/0005600 Decentralized: SK/H/0260/001-005 National Procedure in Portugal: 22/H/0046/001-005
Brief Description of the Product	Chemical class: It is a member of thiophenes, an organochlorine compound, an oxazolidinone, a member of morpholines, a lactam, an aromatic amide and a monocarboxylic acid amide. [1] 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: Not applicable

Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier
Indication(s) in the EEA	Current <u>For EMEA/H/C/0005600, SK/H/0260/001-005 and 22/H/0046/001-005:</u> <u>2.5 mg film-coated tablets</u> 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 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. <u>10 mg film-coated tablets</u> 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. <u>15 mg film-coated tablets</u> <u>Adults</u> Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

	Paediatric population Treatment of venous thromboembolism (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 20 mg film-coated tablets Adults Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. *Paediatric population* Treatment of venous thromboembolism (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 15 mg film-coated tablets and 20 mg film-coated tablets (treatment initiation pack) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Proposed (if applicable): None
Dosage in the EEA	Current For EMEA/H/C/0005600, SK/H/0260/001-005 and 22/H/0046/001-005: 2.5 mg film-coated tablets The recommended dose is 2.5 mg twice daily.

	ACS (Acute coronary syndrome) Patients taking rivaroxaban 2.5 mg twice daily should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. *CAD/PAD* Patients taking rivaroxaban 2.5 mg twice daily should also take a daily dose of 75 – 100 mg ASA. *ACS, CAD/PAD* *Co-administration with antiplatelet therapy* In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Rivaroxaban 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen. 10 mg film-coated tablets *Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery* The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE* 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. 15 mg film-coated tablets *Prevention of stroke and systemic embolism* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*

	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. *Treatment of VTE and prevention of VTE recurrence in children and adolescents* Rivaroxaban treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment. The dose for children and adolescent is calculated based on body weight. - 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. - For patients with body weight less 30 kg refer to the Summary of Product Characteristics of more suitable forms of rivaroxaban. 20 mg film-coated tablets *Prevention of stroke and systemic embolism* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE* 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. *Treatment of VTE and prevention of VTE recurrence in children and adolescents* Rivaroxaban treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment The dose for children and adolescent is calculated based on body weight.

	- 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. - For patients with body weight less 30 kg refer to the Summary of Product Characteristics of more suitable forms of rivaroxaban. <u>15 mg film-coated tablets and 20 mg film-coated tablets (treatment initiation pack)</u> *<u>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE</u>* 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. Proposed (if applicable): None.
Pharmaceutical Form(s) and Strengths	Current 2.5 mg, 10 mg, 15 mg and 20 mg and combination pack (15 mg + 20 mg) film-coated tablets. Proposed (if applicable): None.
Is/will the Product Be Subject to Additional Monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

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

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Viatris has approved RMP(s) for rivaroxaban generic medicine for Centralized procedure: EMEA/H/C/0005600, Decentralized procedure (SK/H/0260/001-005) and National procedure in Portugal (22/H/0046/001-005).

Table 2: SVII- Summary of safety concerns

	RMP 1 (Centralized: EMEA/H/C/0005600, Approval Date: 12-Nov-2021)	**RMP 2 (Decentralized: SK/H/0260/001-005, Approval Date: 10-Mar-2022)**	**RMP 3 (National procedure in Portugal, 22/H/0046/001-005, Approval Date:13-Mar-2023)**
Important Identified Risks	• Haemorrhage	• Haemorrhage	• Haemorrhage
Important Potential Risks	• Embryo-fetal toxicity	• Embryo-fetal toxicity	• Embryo-fetal toxicity
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) • Patients < 18 years	• 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) • Patients < 18 years	• 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) • Patients < 18 years

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension is a potential risk in brand leader RMP. However, it was not considered as a potential risk as Viatris doesn't hold marketing authorization for oral suspension formulation.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Following risk were previously classified as missing information and are being removed from the list of safety concerns in line with reference product RMP (Xarelto EU RMP version 13.4 dated 13-Jun-2022, by Bayer)

- 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)
- 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.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable as this core RMP for rivaroxaban follows the same safety concerns as the safety concerns of the reference product RMP.

SVII.3.2. Presentation of the Missing Information

Not applicable as this core RMP for rivaroxaban follows the same safety concerns as the safety concerns of the reference product RMP.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Haemorrhage
Important potential risks	• Embryo-fetal toxicity
Missing information	• Remedial pro-coagulant therapy for excessive haemorrhage • Patients with atrial fibrillation (AF) and a prosthetic heart valve

PART III: PHARMACOVILIGANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and/or characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for risks:

1. Patients with severe renal impairment (CrCl < 30 mL/min)
2. Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

The forms are provided in Annex 4 of the RMP.

III.2 Additional Pharmacovigilance Activities

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

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The safety information in the proposed product information is aligned to the reference medicinal product (Xarelto, by Bayer).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 4: Part V.1- Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Haemorrhage	Routine risk communication: SmPC sections 4.3, 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation to use with caution in conditions with increased risk of haemorrhage and discontinuation of administration if severe haemorrhage occurs is given in section 4.4. PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM
Embryo-fetal toxicity	Routine risk communication: SmPC sections 4.3, 4.6 and 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk communication: SmPC section 4.9 PL section 3

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: Medicine's legal status: POM

V.2 Additional Risk Minimisation Measures

This medicine has additional risk minimisation measures for the risk Haemorrhage. The additional risk minimisation measures consist of: Educational material for prescribers and Patient Alert Card.

Objectives of Additional Risk Minimisation Activities:

To address the risk of haemorrhage the MAH proposes educational material for prescribers to educate HCPs about specific risk, its early symptoms and the best course of action to be taken when these appear, beyond the recommendation contained in the Product Information.

To address the risk of haemorrhage, the MAH proposes Patient Alert Card to ensure that special information regarding the patient's current therapy and its important risks is held by the patient at all times and reaches the relevant HCP as appropriate. It contains the minimum necessary information to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency.

Rationale for the Additional Risk Minimisation Activity:

The MAH considers it is necessary to educate HCPs and/patients/caregivers about specific risks, and/or their early symptoms and/or the best course of action to be taken when these appear beyond the recommendation contained in the Product Information.

Target Audience and Planned Distribution Path:

HCP/patients/carers

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of additional RMMs will be evaluated on annual basis after MA approval.

Results of Effectiveness Evaluation

After evaluation of all information available to Viatris within the period from 22-Sep-2021 to 21-Sep-2022, including ICSRs from Viatris' global safety database, global literature, PSUR outcome, outcome of signal detection activities, health authority websites, results of interventional and non-interventional studies and EudraVigilance data, no new significant data have become available that may change the safety or benefit-risk profile of rivaroxaban. The risk minimization measures in place for this product are considered adequate and no further actions are needed for the time being.

V.3 Summary of risk minimisation measures

Table 5: Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Haemorrhage	Routine risk minimization measures Additional risk minimisation measures: Educational material for prescribers and Patient Alert Card	Routine pharmacovigilance activities
Embryo-fetal toxicity	Routine risk minimization measures Additional risk minimisation measures: None	Routine pharmacovigilance activities
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimization measures Additional risk minimisation measures: None	Routine pharmacovigilance activities
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimization measures Additional risk minimisation measures: None	Routine pharmacovigilance activities

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Rivaroxaban

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

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

This summary of the RMP for Rivaroxaban should be read in the context of all the 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 Rivaroxaban 's RMP.

I. The Medicine and What it is Used For

Rivaroxaban 2.5 mg, 10 mg, 15 mg, 20 mg, 15 mg and 20 mg (treatment initiation pack) film-coated tablets is authorised for:

Rivaroxaban 2.5 mg film-coated tablets, 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. Rivaroxaban 2.5 mg film-coated tablets 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.

Rivaroxaban 10 mg film-coated tablets is indicated 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.

Rivaroxaban 15 mg film-coated tablets and Rivaroxaban 20 mg film-coated tablets is indicated for: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. Treatment of venous thromboembolism (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.

Rivaroxaban 15 mg film-coated tablets and 20 mg film-coated tablets (Treatment initiation pack) is indicated for: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

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

Further information about the evaluation of Rivaroxaban's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/rivaroxaban-mylan.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Rivaroxaban, together with measures to minimise such 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 public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events 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 Rivaroxaban is not yet available, it is listed under 'missing information' below.

In the case of Rivaroxaban, these routine measures are supplemented with additional risk minimisation measures, mentioned under relevant risks below.

II.A List of Important Risks and Missing Information

Important risks of Rivaroxaban are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. 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. 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/use in special patient populations etc.);

Table 6: Part VI.1- Summary of safety concerns

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

II.B Summary of Important Risks

Table 7: Part VI.2- Important Identified Risk: Haemorrhage

Risk Minimisation Measures	**Routine risk minimisation measures** SmPC Section 4.3, 4.4 and 4.8 PL sections 2 and 4 Prescription-only medicine Limited pack sizes **Additional risk minimisation measures** Educational material for prescribers Patient alert cards

Table 8: Part VI.3- Important Potential Risk: Embryo-fetal toxicity

Risk Minimisation Measures	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.6 and 5.3 PL section 2 Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None

Table 9: Part VI.4- Missing Information: Remedial pro-coagulant therapy for excessive haemorrhage

Risk Minimisation Measures	**Routine risk minimisation measures:** SmPC Section 4.9 PL section 3 Prescription-only medicine Limited pack sizes **Additional risk minimisation measures:** None

Table 10: Part VI.4- Missing Information: Patients with atrial fibrillation (AF) and a prosthetic heart valve

Risk Minimisation Measures	**Routine risk minimisation measures:** SmPC Section 4.4 PL section 2 Prescription-only medicine

	Limited pack sizes **Additional risk minimisation measures:** 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.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Rivaroxaban.

PART VII: ANNEXES

Annex 1 – EudraVigilance Interface

Available in electronic format only.

Annex 2 – Tabulated Summary of Planned, On-going 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

Specific adverse reaction follow-up questionnaires for risks:

1. Patients with severe renal impairment (CrCl < 30 mL/min)
2. Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)

TARGETED FOLLOW UP FORM
Viatris Case No.:

For Patients with significant liver diseases

Dear Reporter,

This questionnaire has been sent to you in order for Viatris to collect more detailed information regarding the adverse event that you reported in relation to Rivaroxaban. Your contribution will be of significant help in improving the knowledge of the safety profile of our drug and in minimizing the risk for patients.
If the information noted below is correct, please sign and date this page at the bottom. If it is not correct, please place a line through the incorrect information and enter the corrected information.

Thank you very much for your cooperation.

1. Patient Information:

Patient's Initials or other identifier		
Date of birth DOB (DD/MM/YY)		
Gender	□ M	□ F
Race	□ Caucasian	□ Black
	□ Asian	□ Hispanic
	□ Other (please specify):	
Weight (kg/lbs)		
Height (cm/in)		

Report type

Study:	□ No	□ Yes	If yes, please specify:	Study number: Patient number:
Spontaneous:	□ No	□ Yes		

2. Indication/prescription for Rivaroxaban:

□ VTE prevention in major orthopedic surgery of the lower limbs

□ Total hip replacement	□ Total knee replacement	□ other (please specify):
□ Stroke prevention in atrial fibrillation		
□ VTE treatment (and secondary prevention)		
□ Other (please specify):		
□ Unknown		

3. Rivaroxaban treatment (total daily dose)

□ 10 mg □ 15 mg □ 20 mg □ 30 mg □ Other □ Unknown			
Start (DD/MM/YY):	□ Unknown	Stop (DD/MM/YY):	□ Unknown
Start after major orthopedic surgery(hours/days):			□ Unknown
Rivaroxaban was discontinued due to the event	□ Yes	□ No	□ Unknown
Rivaroxaban was restarted due to the event	□ Yes	□ No	□ Unknown
Rivaroxaban dose changed	□ Yes Please specify daily dose and start date: Dose (mg): Start date (DD/MM/YY):	□ No	□ Unknown
Patient already switched from □ or to □ another antithrombotic therapy? □ yes □ no □ unknown Date of switch (DD/MM/YY): Drug name and daily dose:			

4. Liver-related adverse event (please specify):

Start/stop date	Start (DD/MM/YY):	□ Unknown	Stop (DD/MM/YY):	□ Unknown
Symptoms and signs of liver injury	□ asthenia/weakness □ Fatigue/tiredness □ Jaundice □ Dark urine □ Pruritus □ Spider nevi □ Confusion □ Coma □ Hepatomegaly □ Splenomegaly □ Ascites □ Other (please specify):			
Diagnostic tests (please provide results)	□ Ultrasound □ Liver biopsy	□ CT □ Autopsy	□ MRI □ ERCP	
Outcome	□ Recovered □ Recovering □ Recovered with sequelae □ Not recovered □ Unknown □ Fatal (autopsy: □ yes □ no □ Unknown)			
Treatment	□ Unknown □ No □ Yes (please specify):			

5. Relevant medical history/risk factors (please tick all relevant boxes)

Active malignancy (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Liver metastasis	□ Unknown	□ No	□ Yes, since when:
Fatty liver	□ Unknown	□ No	□ Yes, since when:
Liver cirrhosis/fibrosis	□ Unknown	□ No	□ Yes, since when:
Viral hepatitis (if yes, please specify):	□ Unknown	□ No	□ Yes, please specify when:
Hepatitis vaccination (if yes, please specify):	□ Unknown	□ No	□ Yes, please specify when:
Biliary disease (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Pancreatitis (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Inherited disease (if yes, please specify	□ Unknown	□ No	□ Yes, since when:

e.g., hemochromatosis, Morbus Wilson,alpha-1-antitrypsin deficiency):			
Autoimmune disease (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Diabetes mellitus Type I or Type II (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Heart failure	□ Unknown	□ No	□ Yes, since when:
Alcohol (please specify quantity in units/day e.g. 1 drink-1unit):	□ Unknown	□ No	□ Yes, since when:
Surgery (if yes, please specify): Type of surgery: Type of anesthesia:	□ Unknown	□ No	□ Yes, please specify when:
Other (please specify)	□ Unknown	□ No	□ Yes, since when:

6. Concomitant medication

Please pay special attention to any potential hepatotoxic drugs/substances such as:

Name of drug	**Total daily dose**	**Start date DD/MM/YY**	**Stop date DD/MM/YY**	**Ongoing**
□ Paracetamol (Acetaminophen)				□ Yes □ No □ Unknown
□ Halothane				□ Yes □ No □ Unknown
□ Methotrexate				□ Yes □ No □ Unknown
□ Amiodarone				□ Yes

				□ No □ Unknown
□ Antibiotics (please specify):				□ Yes □ No □ Unknown
□ NSAIDs (e.g., Diclofenac, Ibuprofen) (please specify):				□ Yes □ No □ Unknown
□ Herbal substances (please specify):				□ Yes □ No □ Unknown
□ Cancer therapy (please specify):				□ Yes □ No □ Unknown
□ Others (please specify):				□ Yes □ No □ Unknown

7. Laboratory data (please fill in or enclose copies of relevant data results)

		Before start of drug						**Normalised after end of drug?**
Lab test:	**Units/ Normal range**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**
ALT (GPT)								□ Yes □ No □ Unknown
AST (GOT)								□ Yes □ No

								□ Unknown
GGT								□ Yes □ No □ Unknown
Alkaline phosphatase								□ Yes □ No □ Unknown
Total bilirubin								□ Yes □ No □ Unknown
Conjugated Bilirubin								□ Yes □ No □ Unknown
CHE								□ Yes □ No □ Unknown
Albumin								□ Yes □ No □ Unknown
Amylase								□ Yes □ No □ Unknown
Lipase								□ Yes □ No

								□ Unknown
LDH/HbdH								□ Yes □ No □ Unknown
PT/INR								□ Yes □ No □ Unknown
Eosinophils								□ Yes □ No □ Unknown

Laboratory data for hepatitis A, B, C, D or E, CMV, EBV, Adenovirus, Coxsackie, Herpes simplex virus, Brucellosis, Leptospirosis, Toxoplasmosis etc. (please fill in or enclose copies of relevant lab data results)			
Lab test	**Units/Normal range**	**Date of investigation DD/MM/YY**	**Results**
			□ Pos □ Neg □ Pending □ Not done □ Unk
			□ Pos □ Neg □ Pending □ Not done □ Unk
			□ Pos □ Neg □ Pending □ Not done □ Unk
			□ Pos □ Neg □ Pending □ Not done □ Unk

Laboratory data for autoimmune diseases (please fill in or enclose copies of relevant lab data results e.g. Antinuclear Ab (ANA), Anti-smooth muscle Ab (SMA), Anti-mitochondrial Ab, Anti-LKM1, Atypical pANCA, etc.)			
Lab test	**Units/Normal range**	**Date of investigation DD/MM/YY**	**Results**
			□ Pos □ Neg □ Pending □ Not done □ Unk

			□ Pos □ Neg □ Pending □ Not done □ Unk
			□ Pos □ Neg □ Pending □ Not done □ Unk

Please enclose also copies of all relevant information (e.g., hospital summary, results of diagnostic tests, e.g., ultrasound, CT, histopathology report of liver biopsy etc.)

8. Reporter's Details:

Name:_____ Address:_____

City:__State:_ Zip Code:____ Country:_____Telephone:_____

Are you the Health Care Provider? No □ Yes □ (If yes, please specify:___)

Sign: Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Please be aware that information provided to Vatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Additional Information: _____

TARGETED FOLLOW UP FORM
Viatris Case No.:

For Patients with severe renal impairment

Dear Reporter,
This questionnaire has been sent to you in order for Viatris to collect more detailed information regarding the adverse event that you reported in relation to Rivaroxaban. Your contribution will be of significant help in improving the knowledge of the safety profile of our drug and in minimizing the risk for patients.

If the information noted below is correct, please sign and date this page at the bottom. If it is not correct, please place a line through the incorrect information and enter the corrected information.
Thank you very much for your cooperation.

9. Patient Information:

Patient's Initials or other identifier		
Date of birth DOB (DD/MM/YY)		
Gender	□ M	□ F
Race	□ Caucasian	□ Black
	□ Asian	□ Hispanic
	□ Other (please specify):	
Weight (kg/lbs)		
Height (cm/in)		

Report type

Study:	□ No	□ Yes	If yes, please specify:	Study number: Patient number:
Spontaneous:	□ No	□ Yes		

10. Indication/prescription for Rivaroxaban:

□ VTE prevention in major orthopedic surgery of the lower limbs		
□ Total hip replacement	□ Total knee replacement	□ other (please specify):
□ Stroke prevention in atrial fibrillation		
□ VTE treatment (and secondary prevention)		

□ Other (please specify):
□ Unknown

11. Rivaroxaban treatment (total daily dose)

□ 10 mg □ 15 mg □ 20 mg □ 30 mg □ Other □ Unknown			
Start (DD/MM/YY):	□ Unknown	Stop (DD/MM/YY):	□ Unknown
Start after major orthopedic surgery(hours/days):			□ Unknown
Rivaroxaban was discontinued due to the event	□ Yes	□ No	□ Unknown
Rivaroxaban was restarted due to the event	□ Yes	□ No	□ Unknown
Rivaroxaban dose changed	□ Yes Please specify daily dose and start date: Dose (mg): Start date (DD/MM/YY):	□ No	□ Unknown
Patient already switched from □ or to □ another antithrombotic therapy? □ yes □ no □ unknown Date of switch (DD/MM/YY): Drug name and daily dose:			

12. Renal-related adverse event (please specify):

Start/stop date	Start (DD/MM/YY):	□ Unknown	Stop (DD/MM/YY):	□ Unknown
Symptoms and signs of renal injury	□ Oliguria □ Hematuria □ Anuria □ Other (please specify):	□ Back pain □ Dysuria □ Fever		□ Polyuria □ Hypertension
Diagnostic procedures (please provide results)	□ Ultrasound □ MRI	□ CT □ Renal biopsy		□ Autopsy
Outcome	□ Recovered □ Not recovered □ Fatal (autopsy: □ yes □ no □ Unknown)	□ Recovering □ Unknown		□ Recovered with sequelae

Treatment	□ Unknown □ No □ Yes (please specify):

13. Relevant medical history/risk factors (please tick all relevant boxes)

Hypertension	□ Unknown	□ No	□ Yes, since when:
Infection (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Glomerulonephritis	□ Unknown	□ No	□ Yes, since when:
Interstitial nephritis	□ Unknown	□ No	□ Yes, please specify when:
Diabetes mellitus □ Type I □ Type II	□ Unknown	□ No	□ Yes, since when:
Autoimmune disease (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Active malignancy (if yes, please specify):	□ Unknown	□ No	□ Yes, since when:
Renal tumour	□ Unknown	□ No	□ Yes, since when:
Surgery (if yes, please specify): Type of surgery: Type of anesthesia: Hypotension during surgery:	□ Unknown	□ No	□ Yes, please specify when:
Other (please specify)	□ Unknown	□ No	□ Yes, since when:

14. Concomitant medication

Please pay special attention to any drugs/substances with known renal side effects such as:

Name of drug	Total daily dose	Start date DD/MM/YY	Stop date DD/MM/YY	Ongoing
□ NSAIDs				□ Yes □ No □ Unknown
□ ACE inhibitors (please specify):				□ Yes □ No □ Unknown
□ Contrast agents (please specify):				□ Yes □ No □ Unknown
□ Antibiotics				□ Yes

(please specify):				□ No □ Unknown
□ Cancer therapy (please specify):				□ Yes □ No □ Unknown
□ Herbal substances (please specify):				□ Yes □ No □ Unknown
□ Others (please specify):				□ Yes □ No □ Unknown

15. Laboratory data (please fill in or enclose copies of relevant data results)

		Before start of drug						**Normalised after end of drug?**
Lab test:	**Units/ Normal range**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**	**Date DD/MM/ YY**
Creatinine								□ Yes □ No □ Unknown
GFR								□ Yes □ No □ Unknown
Urea								□ Yes □ No □ Unknown
Potassium (K)								□ Yes □ No □ Unknown
Sodium (Na)								□ Yes □ No □ Unknown
Phosphate								□ Yes □ No □ Unknown
Calcium								□ Yes □ No

								□ Unknown
Albumin								□ Yes □ No □ Unknown
CRP								□ Yes □ No □ Unknown
Leukocytes								□ Yes □ No □ Unknown
LDH/HbdH								□ Yes □ No □ Unknown
Blood gas analysis								
pH								□ Yes □ No □ Unknown
Bicarbonate								□ Yes □ No □ Unknown
Oxygen								□ Yes □ No □ Unknown
Urinary analysis/Sediment: □ Not done								
Proteinuria								□ Yes □ No □ Unknown
Hematuria								□ Yes □ No □ Unknown
Leukocyturia								□ Yes □ No □ Unknown
Dismorph erythrocytes								□ Yes □ No □ Unknown

Casts/other								□ Yes □ No □ Unknown

Other relevant lab data: (antibodies, urinary or serum eosinophils etc.) Date (DD/MM/YY):

Please enclose also copies of all relevant information (e.g. hospital summary, results of diagnostic tests, histopathology of renal biopsy etc.)

16. Reporter's Details:

Name:_____ Address:_____

City:__State:_ Zip Code:____ Country:_____
Telephone:_____
Are you the Health Care Provider? No□Yes□ (If yes, please specify:_____)

Sign:

Date:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Additional Information: _____

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)

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe rivaroxaban. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with rivaroxaban and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III of the PI]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
  - The need to inform Health Care Professionals that they are taking rivaroxaban if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in the PI.

Annex 7 - Other Supporting Data (Including Referenced Material)

[1] https://pubchem.ncbi.nlm.nih.gov/compound/Rivaroxaban, [Online].

Annex 8 – Summary of Changes to the Risk Management Plan Over Time

Table 11: Annex 8- Summary of Changes to Risk Management Plan Over Time

Version	Approval date	Procedure	Change
0.1	Not applicable	EMEA/H/C/0005600 National MA in PT	Initial submission
	N/A	SK/H/0260	N/A (Initial RMP)
0.2	Not applicable	EMEA/H/C/0005600 National MA in PT	The RMP amended as requested in day 94 PRAC rapporteur RMP assessment report: Included Specific Adverse Reaction Follow-up Questionnaires
	N/A	SK/H/0260	Implementation of Specific Adverse Reaction Follow-up Questionnaires concerning liver-related adverse events and renal impairment/renal failure as part of the routine pharmacovigilance in line with the originator as requested in RMS Day 70 Preliminary Assessment Report for rivaroxaban procedure number SK/H/0260/001-005/DC, dated 26-Feb-2021. Updated invented name and additional monitoring status in EU to 'No'.
0.3	Not applicable	EMEA/H/C/0005600 National MA in PT	The RMP amended as requested in day 150 assessment report
0.4	Not applicable	EMEA/H/C/0005600, SK/H/0260/001-005/DC National MA (22/H/0046/001-005) in PT	Core RMP is prepared to harmonise the RMPs of all rivaroxaban marketing authorisations for which the Viatris has an approved RMP. RMP has been updated in line with reference product RMP (Xarelto EU RMP version 13.4 dated 13-Jun-2022, by Bayer), by removing the following safety concerns (classified as 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) - 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.