

EU Risk Management Plan for INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets (rivaroxaban)

RMP version to be assessed as part of this application	
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Rationale for submitting an updated RMP	The RMP is updated to aligned the list of safety concerned and the risk minimisation measure to the XARELTO ones included in the last RMP revision n 13.4 published on 18/01/2023.
Summary of significant changes in this RMP	<ul style="list-style-type: none">- Update of sections Part I Product overview, Part II Safety specification, Part III Pharmacovigilance Plan , Part V.2 Additional Risk Minimisation Measures, Part VI Summary of the risk management plan section II.A List of important risks and missing information and II.C Post-authorisation development plan, in order to include the brand name of product (approved name INDIFAXA);- Update of Part I Product overview to remove the status of product under additional monitoring- Update of Part II- Module SVIII - Summary of the safety concerns, Part V.1. Routine Risk Minimisation Measures, Part V.3 Summary of risk minimisation measures , Part VI II.A List of important risks and missing information and II.B Summary of important risks in order to align the list of safety concerns to those included in XARELTO RMP last review- Update of III.1 Routine pharmacovigilance activities and Annex 4 in order to include the Follow Up questionnaire for the Liver Related Adverse Event and for Renal Failure
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QPPV name	Marta Laurenza	
QPPV signature		Date: 2023-11-06

Contact person for this RMP Marta Laurenza – EUQPPV of Errekappa Euroterapici
Sara Moretti - Deputy EUQPPV of Errekappa Euroterapici

E-mail address or telephone pharmacovigilance@direnzo.biz

Number of contact person + 39 0677209020

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Rivaroxaban
Pharmacotherapeutic group(s) (ATC Code)	B01AF01
Marketing Authorisation Applicant	Errekappa Euroterapici S.p.A.
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	INDIFAXA, 10 mg, film-coated tablets INDIFAXA, 15 mg, film-coated tablets INDIFAXA, 20 mg, film-coated tablets
Marketing authorisation procedure	National generic application (art. 10.1)
Brief description of the product	<p>Chemical class</p> <p>Rivaroxaban is a morpholine and thiophene derivative that functions. The chemical name of rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxzolidin-5-yl)methyl}-2-thiophene-carboxamide. It is a white to yellowish powder and have following molecular formula : C₁₉H₁₈ClN₃O₅S and molecular weight of 435.879 g/mol (PubChem, 2018).</p> <p>Summary of mode of action</p> <p>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 (Xarelto, SmPC, 2023).</p> <p>Important information about its composition</p> <p>Active substances are chemically synthesized and are provided by qualified Active Pharmaceutical Ingredient (API) manufacturers. The quality of active substance is assured by specification presented in</p>

	module 3.2.S.4.1 of Module 3. The finished drug product is manufactured by Good Manufacturing Practice (GMP)-certified plants.
Hyperlink to the Product Information	eCTD part 1.3.1.
Indication(s) in the EEA	<p>Current (if applicable):</p> <p><u>Rivaroxaban, 10 mg, film-coated tablets:</u></p> <p>Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.</p> <p>Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.</p> <p><u>Rivaroxaban, 15 mg, film-coated tablets:</u></p> <p>Adults</p> <p>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.</p> <p>Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.</p> <p>Paediatric population</p> <p>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.</p> <p><u>Rivaroxaban, 20 mg, film-coated tablets:</u></p> <p>Adults</p> <p>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.</p> <p>Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.</p>

	<p>Paediatric population</p> <p>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.</p> <p>Proposed (if applicable): not applicable.</p>
<p>Dosage in the EEA</p>	<p>Current (if applicable):</p> <p><u>Rivaroxaban, 10 mg, film-coated tablets:</u></p> <p><i>Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery</i></p> <p>The recommended dose is 10 mg rivaroxaban taken orally once daily.</p> <p><i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE</i></p> <p>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.</p> <p><u>Rivaroxaban, 15 mg, film-coated tablets:</u></p> <p><i>Prevention of stroke and systemic embolism in adults</i></p> <p>The recommended dose is 20 mg once daily, which is also the recommended maximum dose.</p> <p><i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults</i></p> <p>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.</p> <p><i>Treatment of VTE and prevention of VTE recurrence in children and adolescents</i></p> <p>Indifaxa treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment.</p> <p>The dose for children and adolescent is calculated based on body weight.</p>

	<ul style="list-style-type: none"> - 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 another medicinal product in granules for oral suspension. <p><u>Rivaroxaban, 20 mg, film-coated tablets:</u></p> <p><i>Prevention of stroke and systemic embolism in adults</i></p> <p>The recommended dose is 20 mg once daily, which is also the recommended maximum dose.</p> <p><i>Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults</i></p> <p>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.</p> <p><i>Treatment of VTE and prevention of VTE recurrence in children and adolescents</i></p> <p>Indifaxa treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment.</p> <p>The dose for children and adolescent is calculated based on body weight.</p> <ul style="list-style-type: none"> - Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose. - Body weight from 30 to 50 kg: a once daily dose of 15 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 another medicinal product in granules for oral suspension.
	Proposed (if applicable): not applicable.
Pharmaceutical form(s) and	Current (if applicable):

strengths	Pharmaceutical form: film-coated tablet
	Strength: 10 mg, 15 mg, 20 mg
	Proposed (if applicable): not applicable.
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)

According to Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

Part II: Module SIII - Clinical trial exposure

According GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

SV.1 Post-authorisation exposure

Not applicable.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

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

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products.

Part II: Module SVII - Identified and potential risks

According to GVP Module V – Risk management systems (Rev 2), this module is not applicable for RMPs submitted with initial marketing authorisation applications involving generic products with no new active substance, if there is a RMP available for the reference medicinal product or when the reference medicinal product does not have an RMP but the safety concerns of the substance are published on the Coordination Group for Mutual Recognition and Decentralised Procedures – Human's (CMDh) website (see part II, Module SVIII).

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

The below safety concerns have been presented in accordance to the Summary of the risk management plan published on the EMA website for the originator medicinal product Xarelto (https://www.ema.europa.eu/en/documents/rmp-summary/xarelto-epar-risk-management-plan_en.pdf).

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 prosthetic heart valve

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

III.1 Routine pharmacovigilance activities

For the proposed identified and potential safety concerns listed in table SVIII.1, routine pharmacovigilance is considered sufficient and currently further pharmacovigilance investigations (i.e., additional activities) are not required.

The safety profile will be constantly monitored through routine pharmacovigilance activities beyond adverse reactions management (including collection, collation and analysis of individual case safety reports) and signal detection, including issue evaluation, literature review, updating of labelling, and liaison with regulatory authorities. Early detection of safety signals enables MA holder to develop and implement appropriate risk management strategy. The objective of the routine surveillance program conducted by the MA holder is to systematically review safety data from multiple sources. The purpose of surveillance is to detect and evaluate changes in reporting frequency of AEs and changes in overall adverse event pattern suggestive of potentially new safety concerns.

The routine pharmacovigilance practices comply with the pharmacovigilance practices covered in Directive 2010/84/EU and Regulation EU 1235/2010 and the associated "Guidelines on good pharmacovigilance practices (GVP)".

Specific adverse reaction follow-up questionnaires for safety concerns:

i. LIVER-RELATED ADVERSE EVENTS

ii. RENAL IMPAIRMENT/RENAL FAILURE.

The mentioned targeted follow up are in place to obtain structured information including detailed descriptions of symptoms and diagnosis, laboratory tests values and concomitant conditions of the patients administered with rivaroxaban. The complete follow up forms are provided in the Annex 4 of this RMP.

Other forms of routine pharmacovigilance activities for safety concerns:

No other forms of routine pharmacovigilance activities are in place beyond the ones proposed in this

section

III.2 Additional pharmacovigilance activities

Together with routine pharmacovigilance activities, additional pharmacovigilance measures are supplemented with the aim to minimize the risks related to the administration of INDIFAXA. Particularly, the MAH provides an educational pack prior to launch, targeting all physicians who are expected to prescribe/use 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 contains:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards.

Moreover, it should be mentioned, that according to the List of medicinal products under additional monitoring from 28.02.2018 (EMA/245297/2013 Rev.53), the reference medicinal product, Xarelto, has been included to the list in July 2013 due to PASS. This PASS was requested after the Bayer Pharma AG, Marketing Authorisation Holder (MAH) of the reference medicinal product Xarelto, submitted on 22 December 2011 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Xarelto in the following indication: "Prevention of cardiovascular death, myocardial infarction and stent thrombosis in patients after an acute coronary syndrome (ACS) (non-ST elevation or ST elevation myocardial infarction or unstable angina) in combination with acetylsalicylic acid (ASA) alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine)"(Xarelto, Assessment Report, 2013). Current application for INDIFAXA 10mg, 15 mg, 20 mg, film-coated tablets does not concern this indication. Therefore, abovementioned PASS is not applicable for INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets as additional pharmacovigilance activity or a condition of marketing authorisation.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Not applicable, efficacy of rivaroxaban in the proposed indication currently do not require further investigation.

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

Safety concern	Routine risk minimisation activities
Important identified risks	
Haemorrhage	<p>Routine risk communication:</p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.4, 4.5, 4.6, 4.8, 4.9</p> <p>PL section 2, 3, 4</p> <p>Other routine risk minimisation measures beyond the Product Information:</p> <p>Legal status: medicinal product is subject to medical prescription</p>
Important potential risks	

Safety concern	Routine risk minimisation activities
Embryo-fetal toxicity	<p>Routine risk communication:</p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.6, 5.3</p> <p>PL section 2</p> <p>Other routine risk minimisation measures beyond the Product Information:</p> <p>Legal status: medicinal product is subject to medical prescription</p>
Missing information	

Safety concern	Routine risk minimisation activities
Remedial pro-coagulant therapy for excessive haemorrhage	<p>Routine risk communication:</p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.9</p> <p>Routine risk minimisation activities recommending specific clinical measures to address the risk:</p> <p>Additional information provided for Management of bleeding</p> <p>Other routine risk minimisation measures beyond the Product Information:</p> <p>Legal status: medicinal product is subject to medical prescription</p>
Patients with AF (atrial fibrillation) and a prosthetic heart valve	<p>Routine risk communication:</p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.4</p> <p>PL section 2</p> <p>Other routine risk minimisation measures beyond the Product Information:</p> <p>Legal status: medicinal product is subject to medical prescription</p>

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1: Prescriber Guide

Objectives:

Prescriber Guide is aimed at increasing awareness about the potential risk of bleeding during treatment with INDIFAXA, 10 mg, 15 mg, 20 mg, film-coated tablets and providing guidance on how to manage that risk.

Rationale for the additional risk minimisation activity:

This additional risk minimisation measure is a condition or restriction with regard to the safe and effective use of the medicinal product implemented by the member states for the reference medicinal product, Xarelto (Bayer Pharma AG).

Target audience and planned distribution path:

To be agreed individually with NCA(s) after granting marketing authorisation and before launching INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets.

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

Effectiveness will be measured using process and outcome indicators (the latter by means of routine pharmacovigilance activities). Criteria for success and milestones will be developed after marketing authorisations for INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets are granted.

Additional risk minimisation 2: Patient Alert Cards

Objectives:

Patient Alert Cards is aimed at increasing awareness about the potential risk of bleeding during treatment with INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets and providing guidance on how to manage

that risk.

Rationale for the additional risk minimisation activity:

This additional risk minimisation measure is a conditions or restrictions with regard to the safe and effective use of the medicinal product implemented by the member states for the reference medicinal product, Xarelto (Bayer Pharma AG).

Target audience and planned distribution path:

To be agreed individually with NCA(s) after granting marketing authorisation and before launching INDIFAXA, 10mg, 15 mg, 20 mg, film-coated tablets.

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

Effectiveness will be measured using process and outcome indicators (the latter by means of routine pharmacovigilance activities). Criteria for success and milestones will be developed after marketing authorisations for INDIFAXA, 10 mg, 15 mg, 20 mg, film-coated tablets are granted.

V.3 Summary of risk minimisation measures

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Important identified risks		
Haemorrhage	<p><u>Routine risk minimisation measures:</u></p> <p><u>Routine risk communication:</u></p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.4, 4.5, 4.6, 4.8, 4.9</p> <p>PL section 2, 3, 4</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Legal status: medicinal product is subject to</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p>

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	<p>medical prescription</p> <p><u>Additional risk minimisation measures:</u></p> <ul style="list-style-type: none"> – Prescriber Guide, – Patient Alert Card 	
Important potential risks		
Embryo-fetal toxicity	<p><u>Routine risk minimisation measures:</u></p> <p><u>Routine risk communication:</u></p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.6, 5.3</p> <p>PL section 2</p> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>Legal status: medicinal product is subject to medical prescription</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p>
Missing information		
Remedial procoagulant therapy for excessive haemorrhage	<p><u>Routine risk minimisation measures:</u></p> <p><u>Routine risk communication:</u></p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.9</p> <p>PL NA</p> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>Legal status: subject to medical prescription</p> <p><u>Additional risk minimisation measures:</u></p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p>

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	None	
Patients with AF (atrial fibrillation) and a prosthetic heart valve	<p><u>Routine risk minimisation measures:</u></p> <p><i>Routine risk communication:</i></p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.4</p> <p>PL section 2</p> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>Legal status: medicinal product is subject to medical prescription</p> <p><u>Additional risk minimisation measures:</u></p> <p>None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>None</p>

Part VI: Summary of the risk management plan

Summary of risk management plan for INDIFAXA, 10 mg, film-coated tablets (rivaroxaban)

This is a summary of the risk management plan (RMP) for INDIFAXA, 10 mg, film-coated tablets. The RMP details important risks of INDIFAXA, 10 mg, film-coated tablets, how these risks can be minimised, and how more information will be obtained about INDIFAXA, 10 mg, film-coated tablets' risks and uncertainties (missing information).

INDIFAXA, 10 mg, film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how INDIFAXA, 10 mg, film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of INDIFAXA, 10 mg, film-coated tablets' RMP.

I. The medicine and what it is used for

INDIFAXA, 10 mg, film-coated tablets is authorised for adults to prevent blood clots in the veins after a hip or knee replacement operation and/or to treat blood clots in the veins of legs (deep vein thrombosis) and in the blood vessels of lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of legs and/or lungs (see SmPC for the full indication). It contains rivaroxaban as the active substance and it is given by mouth (orally).

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

Important risks of INDIFAXA, 10 mg, film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about INDIFAXA, 10 mg, film-coated tablets' 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 INDIFAXA, 10 mg, film-coated tablets, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 INDIFAXA, 10 mg, film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of INDIFAXA, 10 mg, film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INDIFAXA, 10 mg, film-coated tablets. 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).

Table part VI-IIa: List of important risks and missing information

Summary of safety concerns	
Important identified risks	– Haemorrhage
Important potential risks	– Embryo-foetal 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

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

With reference to one safety concern, apart from routine risk minimisation measures, there are some additional risks minimisation measures:

Important identified risk: Haemorrhage	
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p><i>Routine risk communication:</i></p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.4, 4.5, 4.6, 4.8, 4.9</p> <p>PL section 2, 3, 4</p> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>Legal status: medicinal product is subject to medical prescription</p> <p><u>Additional risk minimisation measures:</u></p> <ul style="list-style-type: none">– Prescriber Guide,– Patient Alert Card

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 INDIFAXA, 10 mg, film-coated tablets

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

There are no studies required for INDIFAXA, 10 mg, film-coated tablets.

Summary of risk management plan for INDIFAXA, 15 mg, film-coated tablets (rivaroxaban)

This is a summary of the risk management plan (RMP) for INDIFAXA, 15 mg, film-coated tablets. The RMP details important risks of INDIFAXA, 15 mg, film-coated tablets, how these risks can be minimised, and how more information will be obtained about INDIFAXA, 15 mg, film-coated tablets, risks and uncertainties (missing information).

INDIFAXA, 15 mg, film-coated tablets, summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how INDIFAXA, 15 mg, film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of INDIFAXA, 15 mg, film-coated tablets' RMP.

I. The medicine and what it is used for

INDIFAXA, 15 mg, film-coated tablets is authorised for adults to prevent blood clots in brain (stroke) and other blood vessels in body in patients with a form of irregular heart rhythm called non-valvular atrial fibrillation, and to treat blood clots in the veins of legs (deep vein thrombosis) and in the blood vessels of lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of legs and/or lungs (see SmPC for the full indication). It contains rivaroxaban as the active substance and it is given by mouth (orally).

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

Important risks of INDIFAXA, 15 mg, film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about INDIFAXA, 15 mg, film-coated tablets' 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 INDIFAXA, 15 mg, film-coated tablets, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 INDIFAXA, 15 mg, film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of INDIFAXA, 15 mg, film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INDIFAXA, 15 mg, film-coated tablets. 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).

Table part VI-IIa: List of important risks and missing information

Summary of safety concerns	
Important identified risks	– Haemorrhage
Important potential risks	– Embryo-foetal toxicity
Missing information	– Remedial pro-coagulant therapy for excessive haemorrhage

Summary of safety concerns

- Patients with atrial fibrillation (AF) and a prosthetic heart valve

II.B Summary of important risks

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

With reference to one safety concern, apart from routine risk minimisation measures, there are some additional risks minimisation measures:

Important identified risk: Haemorrhage

Risk minimisation measures

Routine risk minimisation measures:

Routine risk communication:

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

SmPC section 4.3, 4.4, 4.5, 4.6, 4.8, 4.9

PL section 2, 3, 4

Other routine risk minimisation measures beyond the Product Information:

Legal status: medicinal product is subject to medical prescription

Additional risk minimisation measures:

- Prescriber Guide,
- Patient Alert Card

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

INDIFAXA, 15 mg, film-coated tablets

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

There are no studies required for INDIFAXA, 15 mg, film-coated tablets.

Summary of risk management plan for INDIFAXA, 20 mg, film-coated tablets (rivaroxaban)

This is a summary of the risk management plan (RMP) for INDIFAXA, 20 mg, film-coated tablets. The RMP details important risks of INDIFAXA, 20 mg, film-coated tablets, how these risks can be minimised, and how more information will be obtained about INDIFAXA, 20 mg, film-coated tablets, risks and uncertainties (missing information).

INDIFAXA, 20 mg, film-coated tablets, summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how INDIFAXA, 20 mg, film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of INDIFAXA, 20 mg, film-coated tablets' RMP.

I. The medicine and what it is used for

INDIFAXA, 20 mg, film-coated tablets is authorised for adults to prevent blood clots in brain (stroke) and other blood vessels in body in patients with a form of irregular heart rhythm called non-valvular atrial fibrillation, and to treat blood clots in the veins of legs (deep vein thrombosis) and in the blood vessels of lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of legs and/or lungs (see SmPC for the full indication). It contains rivaroxaban as the active substance and it is given by mouth (orally).

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

Important risks of INDIFAXA, 20 mg, film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Rivaroxaban INDIFAXA, 20 mg, film-coated tablets' 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 INDIFAXA, 20 mg, film-coated tablets, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 INDIFAXA, 20 mg, film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of INDIFAXA, 20 mg, film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INDIFAXA, 20 mg, film-coated tablets. 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).

Table part VI-IIa: List of important risks and missing information

Summary of safety concerns	
Important identified risks	– Haemorrhage
Important potential risks	– Embryo-foetal toxicity
Missing information	<ul style="list-style-type: none"> – Remedial pro-coagulant therapy for excessive haemorrhage – Patients with atrial fibrillation (AF) and a prosthetic heart valve

II.B Summary of important risks

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

With reference to one safety concern, apart from routine risk minimisation measures, there are some additional risks minimisation measures:

Important identified risk: Haemorrhage	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>Routine risk communication:</p> <p>The safety information in the proposed product information is aligned to the reference medicinal product.</p> <p>SmPC section 4.3, 4.4, 4.5, 4.6, 4.8, 4.9</p> <p>PL section 2, 3, 4</p> <p>Other routine risk minimisation measures beyond the Product Information:</p> <p>Legal status: medicinal product is subject to medical prescription</p> <p>Additional risk minimisation measures:</p> <ul style="list-style-type: none"> – Prescriber Guide,

Important identified risk: Haemorrhage	
	– Patient Alert Card

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 INDIFAXA, 20 mg, film-coated tablets

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

There are no studies required for INDIFAXA, 20 mg, film-coated tablets.

Part VII: Annexes

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



Questionnaire Liver-Related Adverse Events

SECTION I - REFERENCE ID			
CASE ID:		STUDY / PROJECT ID:	PATIENT ID:
SECTION II - REPORTER/PATIENT INFORMATION			
REPORTER: <input type="radio"/> Physician <input type="radio"/> Nurse <input type="radio"/> Patient <input type="radio"/> Other (specify):			
REPORTER CONTACT INFORMATION			
Name:		Institution/Practice Name:	
Address:			
ZIP Code:	City:	Country:	
Phone:	Fax:	Email:	
PATIENT INFORMATION			
Age [years]: <small>(at onset of event)</small>	Gender: <input type="radio"/> Male <input type="radio"/> Female	Weight [kg]:	Height [cm]:
Race: <input type="radio"/> White <input type="radio"/> Black or African American <input type="radio"/> American Indian/Alaska Native <input type="radio"/> Native Hawaiian/Pacific Islander <input type="radio"/> Asian <input type="radio"/> Other (specify):			
Ethnicity: <input type="radio"/> Hispanic or Latino <input type="radio"/> Not Hispanic or Latino <input type="radio"/> Unknown			
SECTION III - PRODUCT INFORMATION (Rivaroxaban)			
INDICATION			
<input type="radio"/> VTE prevention in Major orthopedic surgery <input type="radio"/> Total hip replacement <input type="radio"/> Total knee replacement <input type="radio"/> Other lower limbs (specify):			
<input type="radio"/> Stroke prevention in atrial fibrillation		<input type="radio"/> VTE treatment (and secondary prevention)	
<input type="radio"/> Other (specify):		<input type="radio"/> 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			
<input type="radio"/> Yes (specify):			<input type="radio"/> No treatment <input type="radio"/> Unknown
SUSPECTED CAUSE OF EVENT			
Related to Rivaroxaban treatment? <input type="radio"/> Yes <input type="radio"/> No (specify alternative explanation/other contributing factors):			

Action taken with Rivaroxaban		Date (dd/mm/yyyy)	
<input type="radio"/> Dose increased	<input type="radio"/> Dose reduced		New dose:
<input type="radio"/> Interrupted		From:	To:
<input type="radio"/> Withdrawn			
<input type="radio"/> None	<input type="radio"/> 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)		
<input type="checkbox"/> Asthenia / Fatigue			
<input type="checkbox"/> Pruritus (itching)			
<input type="checkbox"/> Jaundice			
<input type="checkbox"/> Ascites			
<input type="checkbox"/> Altered level of consciousness encephalopathy			
<input type="checkbox"/> Confusion			
<input type="checkbox"/> Coma			
<input type="checkbox"/> Hepatomegaly			
<input type="checkbox"/> Splenomegaly			
<input type="checkbox"/> Dark Urine			
<input type="checkbox"/> Spider nevi			
<input type="checkbox"/> Other liver-related symptoms and signs (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) 	
Alk. phosphatase							<input type="checkbox"/>
Total bilirubin							<input type="checkbox"/>
Conjugated (direct) bilirubin							<input type="checkbox"/>
ALT / SGPT							<input type="checkbox"/>
AST / SGOT							<input type="checkbox"/>
Gamma GT							<input type="checkbox"/>
PT							<input type="checkbox"/>
INR							<input type="checkbox"/>
Albumin							<input type="checkbox"/>
LDH							<input type="checkbox"/>
HbdH							<input type="checkbox"/>
Complete Blood Count Hemoglobin							<input type="checkbox"/>
Eosinophils							<input type="checkbox"/>
Amylase							<input type="checkbox"/>
Lipase							<input type="checkbox"/>
Creatinine Kinase							<input type="checkbox"/>
Choline Esterase							<input type="checkbox"/>
Other (specify):							<input type="checkbox"/>






Serology test for virus infection	Test date (dd/mm/yyyy)	Results with units	Comments
<input type="checkbox"/> Anti-Hep. A Virus IgM Antibodies			
<input type="checkbox"/> Hepatitis B surface Antigen <input type="checkbox"/> Hepatitis B PCR (viral copies) <input type="checkbox"/> Anti-Hep. B surface Antibodies <input type="checkbox"/> Anti-Hep. B core IgM Antibodies <input type="checkbox"/> Anti-Hep.s B core IgG Antibodies			
<input type="checkbox"/> Anti-Hepatitis C Virus Antibodies <input type="checkbox"/> Anti-Hep. C Virus IgM Antibodies <input type="checkbox"/> Hepatitis C PCR (viral copies)			
<input type="checkbox"/> Anti-Hep. D Virus IgM Antibodies <input type="checkbox"/> Hepatitis D PCR (viral copies)			
<input type="checkbox"/> Anti-Hep. E virus IgG Antibodies <input type="checkbox"/> Anti-Hep. E virus IgM Antibodies <input type="checkbox"/> Hepatitis E virus RNA (PCR)			
<input type="checkbox"/> Anti-Cytomegalovirus (CMV) IgM Antibodies <input type="checkbox"/> Cytomegalovirus (CMV) PCR			
<input type="checkbox"/> Anti-Epstein-Barr Virus (EBV) IgM Antibodies <input type="checkbox"/> EBV other (specify):			
<input type="checkbox"/> Adenovirus IgG <input type="checkbox"/> Adenovirus IgM			
<input type="checkbox"/> Coxsackie IgG <input type="checkbox"/> Coxsackie IgM			
<input type="checkbox"/> Herpes Simplex IgG <input type="checkbox"/> Herpes Simplex IgM			
<input type="checkbox"/> Toxoplasmosis			
<input type="checkbox"/> Brucella (specify):			
<input type="checkbox"/> Leptospira (specify):			
<input type="checkbox"/> Other Serology test (specify):			






Autoimmune markers	Test date (dd/mm/yyyy)	Results with units	Comments			
<input type="checkbox"/> Antinuclear Ab (ANA)						
<input type="checkbox"/> Anti-smooth muscle Ab (SMA)						
<input type="checkbox"/> Anti-mitochondrial Antibodies						
<input type="checkbox"/> Anti-KLM1 Antibodies						
<input type="checkbox"/> Anti-SLA / LP						
<input type="checkbox"/> Atypical p-ANCA						
<input type="checkbox"/> Other autoimmune test (specify):						
Further Investigations	Test date (dd/mm/yyyy)	Short summary of the result				
<input type="checkbox"/> Ultrasound						
<input type="checkbox"/> CT						
<input type="checkbox"/> MRI						
<input type="checkbox"/> ERCP						
<input type="checkbox"/> Liver biopsy						
<input type="checkbox"/> Other (specify):						
SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered <i>hepatotoxic medications</i> including any drugs given up to <u>2 months prior</u> 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?
<input type="checkbox"/> Other antithrombotic therapy						<input type="checkbox"/>
<input type="checkbox"/> Paracetamol						<input type="checkbox"/>
<input type="checkbox"/> Methotrexate						<input type="checkbox"/>
<input type="checkbox"/> Amiodarone						<input type="checkbox"/>
<input type="checkbox"/> NSAIDs (specify):						<input type="checkbox"/>
<input type="checkbox"/> Herbal substances (specify):						<input type="checkbox"/>
<input type="checkbox"/> Antibiotics (specify):						<input type="checkbox"/>
<input type="checkbox"/> Cancer therapy (specify):						<input type="checkbox"/>
<input type="checkbox"/> Halothane						<input type="checkbox"/>
						<input type="checkbox"/>

SECTION VI - MEDICAL HISTORY / RISK FACTORS				
Relevant medical history / Concomitant conditions	Start date (dd/mm/yyyy)	On-going	Stop date (dd/mm/yyyy)	Details
<input type="checkbox"/> Active malignancy		<input type="checkbox"/>		Specify type:
<input type="checkbox"/> Liver cancer / metastases		<input type="checkbox"/>		
<input type="checkbox"/> Liver cirrhosis / fibrosis <input type="checkbox"/> Child-Pugh Class:		<input type="checkbox"/>		
<input type="checkbox"/> Fatty liver		<input type="checkbox"/>		
<input type="checkbox"/> Viral Hepatitis		<input type="checkbox"/>		Specify acute or chronic, type.
<input type="checkbox"/> Hepatis vaccination		N/A	N/A	Specify type:
<input type="checkbox"/> Biliary disease		<input type="checkbox"/>		
<input type="checkbox"/> Pancreatitis		<input type="checkbox"/>		
<input type="checkbox"/> Autoimmune disease (specify):		<input type="checkbox"/>		
<input type="checkbox"/> Hemochromatosis		<input type="checkbox"/>		
<input type="checkbox"/> Wilson's disease		<input type="checkbox"/>		
<input type="checkbox"/> Alpha 1-antitrypsin deficiency		<input type="checkbox"/>		
<input type="checkbox"/> Diabetes mellitus		<input type="checkbox"/>		
<input type="checkbox"/> Heart failure		<input type="checkbox"/>		
<input type="checkbox"/> Renal failure		<input type="checkbox"/>		
<input type="checkbox"/> Alcohol misuse		<input type="checkbox"/>		
<input type="checkbox"/> Surgery		N/A	N/A	Specify type of surgery and type of anesthesia:
<input type="checkbox"/> Other (specify):		<input type="checkbox"/>		
SECTION VII - ADDITIONAL INFORMATION / COMMENTS (if any):				
This section can 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 done	Autopsy details Continue with SECTION IV	
		<input type="checkbox"/>		
<p>Please provide and attach results of any relevant laboratory and diagnostic procedures performed, or any other relevant document, if available.</p>				

Questionnaire Renal Failure

SECTION I - REFERENCE ID			
CASE ID:		STUDY / PROJECT ID:	PATIENT ID:
SECTION II - REPORTER/PATIENT INFORMATION			
REPORTER: <input type="radio"/> Physician <input type="radio"/> Nurse <input type="radio"/> Patient <input type="radio"/> 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: <input type="radio"/> Male <input type="radio"/> Female	Weight [kg]:	Height [cm]:
Race: <input type="radio"/> White <input type="radio"/> Black or African American <input type="radio"/> American Indian/Alaska Native <input type="radio"/> Native Hawaiian/Pacific Islander <input type="radio"/> Asian <input type="radio"/> Other (specify):			
Ethnicity: <input type="radio"/> Hispanic or Latino <input type="radio"/> Not Hispanic or Latino <input type="radio"/> Unknown			
SECTION III - PRODUCT INFORMATION (Rivaroxaban)			
INDICATION			
<input type="radio"/> VTE prevention in Major orthopedic surgery <input type="radio"/> Total hip replacement <input type="radio"/> Total knee replacement <input type="radio"/> Other lower limbs (specify):			
<input type="radio"/> Stroke prevention in atrial fibrillation		<input type="radio"/> VTE treatment (and secondary prevention)	
<input type="radio"/> Other (specify):		<input type="radio"/> Unknown	
Therapy started: [days] 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 RENAL EVENT			
<input type="radio"/> Yes (specify):			<input type="radio"/> No treatment <input type="radio"/> Unknown
SUSPECTED CAUSE OF EVENT			
Related to Rivaroxaban treatment? <input type="radio"/> Yes <input type="radio"/> No (specify alternative explanation/other contributing factors):			

Action taken with Rivaroxaban		Date (dd/mm/yyyy)					
<input type="radio"/> Dose increased	<input type="radio"/> Dose reduced		New dose:				
<input type="radio"/> Interrupted		From:	To:				
<input type="radio"/> Withdrawn							
<input type="radio"/> None		<input type="radio"/> 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)					
<input type="checkbox"/> Oliguria							
<input type="checkbox"/> Hematuria							
<input type="checkbox"/> Fever							
<input type="checkbox"/> Anuria							
<input type="checkbox"/> Dysuria							
<input type="checkbox"/> Polyuria							
<input type="checkbox"/> Back pain							
<input type="checkbox"/> Hypertension							
<input type="checkbox"/> 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)							<input type="checkbox"/>
Creatinine Kinase (CK)							<input type="checkbox"/>
GFR							<input type="checkbox"/>
Urea							<input type="checkbox"/>
Potassium (K)							<input type="checkbox"/>
Sodium (Na)							<input type="checkbox"/>
Phosphate							<input type="checkbox"/>
Calcium							<input type="checkbox"/>
Albumin							<input type="checkbox"/>

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							
CRP							<input type="checkbox"/>
Leukocytes							<input type="checkbox"/>
LDH							<input type="checkbox"/>
HbdH							<input type="checkbox"/>
Blood Gas Analysis							
pH							<input type="checkbox"/>
Bicarbonate							<input type="checkbox"/>
Oxygen							<input type="checkbox"/>
Urinalysis / Sediment							
Proteinuria							<input type="checkbox"/>
Hematuria							<input type="checkbox"/>
Leukocyturia							<input type="checkbox"/>
Dysmorphic erythrocytes							<input type="checkbox"/>
Casts							<input type="checkbox"/>
Other (e.g. antibodies, urinary or serum eosinophils, specify):							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>
Further investigations		Test date (dd/mm/yyyy)		Short summary of the result			
<input type="checkbox"/> Ultrasound							
<input type="checkbox"/> CT							
<input type="checkbox"/> MRI							
<input type="checkbox"/> Renal biopsy							
<input type="checkbox"/> Other (specify):							

SECTION V - RELEVANT CONCOMITANT MEDICATION						
Concomitantly administered drugs with known renal side effects given up to <u>2 months prior</u> 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?
<input type="checkbox"/> Other antithrombotic therapy						<input type="checkbox"/>
<input type="checkbox"/> NSAIDs (specify):						<input type="checkbox"/>
<input type="checkbox"/> ACE inhibitors (specify):						<input type="checkbox"/>
<input type="checkbox"/> Contrast agents (specify):						<input type="checkbox"/>
<input type="checkbox"/> Antibiotics (specify):						<input type="checkbox"/>
<input type="checkbox"/> Cancer therapy (specify):						<input type="checkbox"/>
<input type="checkbox"/> Herbal substances (specify):						<input type="checkbox"/>
						<input type="checkbox"/>
						<input type="checkbox"/>
SECTION VI - MEDICAL HISTORY / RISK FACTORS						
Relevant medical history / Concomitant conditions	Start date (dd/mm/yyyy)	On-going	Stop date (dd/mm/yyyy)	Details		
<input type="checkbox"/> Active malignancy		<input type="checkbox"/>		Specify type:		
<input type="checkbox"/> Renal tumor		<input type="checkbox"/>				
<input type="checkbox"/> Hypertension		<input type="checkbox"/>				
<input type="checkbox"/> Infection (specify):		<input type="checkbox"/>				
<input type="checkbox"/> Glomerulonephritis		<input type="checkbox"/>				
<input type="checkbox"/> Interstitial nephritis		<input type="checkbox"/>				
<input type="checkbox"/> Autoimmune disease (specify):		<input type="checkbox"/>				
<input type="checkbox"/> Diabetes mellitus		<input type="checkbox"/>				
<input type="checkbox"/> Surgery (specify type of surgery, type of anesthesia, hypotension during surgery)		N/A	N/A			
<input type="checkbox"/> Other (specify):		<input type="checkbox"/>				
SECTION VII - ADDITIONAL INFORMATION / COMMENTS (if any):						
This section can 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 done	Autopsy details <i>Continue with SECTION IV</i>			
		<input type="checkbox"/>				

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)

Key messages of the additional risk minimisation measures

Physician educational material:

- The Summary of Product Characteristics
- Guide for healthcare professionals:
 - ☐ 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 provided with a;
 - ☐ Patient alert card and be counselled about:
 - o Signs or symptoms of bleeding and when to seek attention from a health care provider.
 - o Importance of treatment compliance
 - o The need for intake of the 15 mg and 20 mg tablets with food
 - o Necessity to carry the Patient alert card with them at all times
 - o The need to inform Health Care Professionals that they are taking Rivaroxaban if they need to have any surgery or invasive procedure.

-
- Patient alert card:
 - ☐ 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 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 patient information pack:

- Patient information leaflet.

Annex 7 - Other supporting data (including referenced material)

1. Xarelto, EPAR Risk Management Plan Summary:
https://www.ema.europa.eu/en/documents/rmp-summary/xarelto-epar-risk-management-plan_en.pdf
(accessed last on 18th January 2023).
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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
0.0	N.A.	Initial submission by Benedetti and Co
0.1	N.A.	Information is not available
0.2	N.A	Information is not available.
0.3	N.A	The RMP has been updated as a consequence of the MA transfer from Benedetti &co to ERREKAPPA EUROTHERAPICI SPA. Part I, Part II module SVIII, Part III, Part V, Part VI and Annex IV have been updated.
0.4	N.A	<ul style="list-style-type: none"> - Update of sections Part I Product overview, Part II Safety specification, Part III Pharmacovigilance Plan, Part V.2 Additional Risk Minimisation Measures, Part VI Summary of the risk management plan section II.A List of important risks and missing information and II.C Post-authorisation development plan, in order to include the brand name of product (approved name INDIFAXA); - Update of Part I Product overview to remove the status of product under additional monitoring - Update of Part II- Module SVIII - Summary of the safety concerns, Part V.1. Routine Risk Minimisation Measures, Part V.3 Summary of risk minimisation measures, Part VI II.A List of important risks and missing information and II.B Summary of important risks in order to align the list of safety concerns to those included in XARELTO RMP last review - Update of III.1 Routine pharmacovigilance activities and Annex 4 in order to include the Follow Up questionnaire for the Liver Related Adverse Event and for Renal Failure