Summary of risk management plan for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) (Rivaroxaban)

This is a summary of the risk management plan (RMP) for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg). The RMP details important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), how these risks can be minimised, and how more information will be obtained about Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s risks and uncertainties (missing information).

Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) should be used.

This summary of the RMP for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s RMP.

I. The medicine and what it is used for

Rivaroxaban Accord 2.5 mg film coated tablets co administered with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Rivaroxaban Accord, 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 Accord 10 mg film coated tablets is used 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 Accord 15 mg and 20 mg film coated tablets are used 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.

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

Further information about the evaluation of Rivaroxaban Accord 15 mg and 20 mg film coated tablets benefits can be found in < Rivaroxaban Accord 15 mg and 20 mg film coated tablets 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-accord

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

Important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), together with measures to minimise such risks and the proposed studies for learning more about Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s risks, are outlined below.

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

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

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

In the case of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and signal management activity, 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 Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg). 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);

Important identified risks	• Haemorrhage
Important potential risks	• 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

II.B Summary of important risks

Important Identified Risks: **Haemorrhage**	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2, 4.3, 4.4, 4.6 4.8, 4.9 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: • Educational material for prescribers • Patient alert cards

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 Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).

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

There are no studies required for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).

1.8 INFORMATION RELATING TO PHARMACOVIGILANCE

1.8.2 Risk-management System

Enclosed

EU Risk Management Plan for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) (Rivaroxaban)

RMP version to be assessed as part of this application:

RMP Version number	1.3
Data lock point for this RMP	09 September 2020
Date of final sign off	09 September 2020

Rationale for submitting an updated RMP:

To update Risk Management Plan (RMP) as per CHMP Day 195 Joint Assessment Report received on 08 September 2020.

Summary of significant changes in this RMP:

As per PRAC Rapporteur Risk Management Plan (RMP) CHMP Day-195 Joint Assessment Report, Annex 4 has been updated.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

QPPV name: Ms. Agata Gesiewicz

QPPV signature: Agata Gesiewicz

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Part I: Product(s) Overview

Table 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	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	4
Invented name(s) in the European Economic Area (EEA)	Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: Morpholine and thiophene derivative that functions as a Factor Xa Inhibitor.
	Mechanism 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.
	<u>Important information about its composition</u> Each film coated tablet contains 2.5 mg rivaroxaban. <u>Excipient with known effect</u> Each film coated tablet contains 27.90 mg lactose (as

	monohydrate) Each film-coated tablet contains 10 mg rivaroxaban. Excipient with known effect Each film-coated tablet contains 27.90 mg lactose (as monohydrate) Each film-coated tablet contains 15 mg rivaroxaban. Excipient with known effect Each film-coated tablet contains 20.92 mg lactose (as monohydrate) Each film-coated tablet contains 20 mg rivaroxaban. Excipient with known effect Each film-coated tablet contains 27.90 mg lactose (as monohydrate) Tablet core Lactose monohydrate Croscarmellose Sodium (E468) Sodium lauryl sulphate (E487) Hypromellose (E464) Cellulose, microcrystalline (E460) Silica, colloidal anhydrous (E551) Magnesium Stearate (E572) Film coating Macrogol 4000 (E1521)

	Hypromellose (E664) Titanium dioxide (E171) Iron oxide red (E172) (10 mg, 15 mg & 20 mg) Iron oxide yellow (E172) (2.5 mg)
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL
Indication(s) in the EEA Proposed	**Rivaroxaban Accord 2.5 mg film-coated tablets** Rivaroxaban Accord, co administered with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Rivaroxaban Accord, 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 Accord 10 mg film-coated tablets** 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 Accord 15 mg and 20 mg film-coated tablets** 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.
Dosage in the EEA Proposed	**<u>Rivaroxaban Accord 2.5 mg film-coated tablets</u>** <u>Posology</u> The recommended dose is 2.5 mg twice daily. <u>ACS</u> Patients taking Rivaroxaban Accord 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 standard daily dose of ticlopidine. Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited. Treatment with rivaroxaban should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued. <u>CAD/PAD</u> Patients taking Rivaroxaban Accord 2.5 mg twice daily should also take a daily dose of 75-100 mg ASA. Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks. In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Rivaroxaban Accord 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen. Safety and efficacy of Rivaroxaban Accord 2.5 mg twice daily in combination with ASA plus ticlopidine has only

	been studied in patients with recent ACS. Dual antiplatelet therapy has not been studied in combination with Rivaroxaban Accord 2.5 mg twice daily in patients with CAD/PAD. If a dose is missed the patient should continue with the regular dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose. *Converting from Vitamin K Antagonists (VKA) to rivaroxaban* When converting patients from VKAs to rivaroxaban, International Normalised Ratio (INR) values could be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used. *Converting from rivaroxaban to Vitamin K antagonists (VKA)* There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR. In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord is discontinued INR testing may be done reliably at least 24 hours after the last dose. *Converting from parenteral anticoagulants to rivaroxaban* For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0

	to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin). *Converting from rivaroxaban to parenteral anticoagulants* Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken. **Rivaroxaban Accord 10 mg film-coated tablets** Posology *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. The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery. • For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended. • For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended. If a dose is missed the patient should take Rivaroxaban Accord immediately and then continue the following day with once daily intake as before. *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.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Accord 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

	Time period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban Accord

	immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day. If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose. *Converting from Vitamin K Antagonists (VKA) to rivaroxaban* For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5. When converting patients from VKAs to rivaroxaban, International Normalised Ratio (INR) values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used. *Converting from rivaroxaban to Vitamin K antagonists (VKA)* There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR. In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban.

	Once Rivaroxaban Accord is discontinued INR testing may be done reliably at least 24 hours after the last dose. *Converting from parenteral anticoagulants to rivaroxaban* For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin). *Converting from rivaroxaban to parenteral anticoagulants* Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken. **Rivaroxaban Accord 15 mg film-coated tablets** Posology *Prevention of stroke and systemic embolism* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. Therapy with Rivaroxaban Accord should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding. If a dose is missed the patient should take Rivaroxaban Accord immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose. *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.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

	Time period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take Rivaroxaban Accord

	immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day. If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose. *Converting from Vitamin K Antagonists (VKA) to rivaroxaban* For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3.0. For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5. When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used. *Converting from rivaroxaban to Vitamin K antagonists (VKA)* There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR. In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as

	guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord is discontinued INR testing may be done reliably at least 24 hours after the last dose. *Converting from parenteral anticoagulants to rivaroxaban* For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin). *Converting from rivaroxaban to parenteral anticoagulants* Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken. **Rivaroxaban Accord 20 mg film-coated tablets** Posology *Prevention of stroke and systemic embolism* The recommended dose is 20 mg once daily, which is also the recommended maximum dose. Therapy with Rivaroxaban Accord should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding. If a dose is missed the patient should take Rivaroxaban Accord immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

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.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Accord 10 mg once daily, a dose of Rivaroxaban Accord 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

	Time period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

	To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available. If a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take Rivaroxaban Accord immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day. If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose. *Converting from Vitamin K Antagonists (VKA) to rivaroxaban* For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3.0. For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5. When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used. *Converting from rivaroxaban to Vitamin K antagonists (VKA)* There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can

	contribute to an elevated INR. In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord is discontinued INR testing may be done reliably at least 24 hours after the last dose. *Converting from parenteral anticoagulants to rivaroxaban* For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin). *Converting from rivaroxaban to parenteral anticoagulants* Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken. <u>Method of administration</u> Rivaroxaban Accord is for oral use. 2.5 mg and 10 mg film-coated tablets are to be taken with or without food. 15 mg and 20 mg film-coated tablets are to be taken with food. For patients who are unable to swallow whole tablets, Rivaroxaban Accord tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban Accord

	15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food. The crushed Rivaroxaban Accord tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban Accord 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding
Pharmaceutical form(s) and strengths Proposed	Film-coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)
Is the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

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

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

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

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

There is a summary available for the reference medicinal product Xarelto® (Rivaroxaban) RMP version 11.4 with Data lock point (DLP) dated 01-Aug-2018 on EMA website.

There is no change proposed by MAH in these safety concerns mentioned in Module SVIII of this RMP which in-line with the RMP summary for reference product Xarelto® (Rivaroxaban).

Hence this section remains “Not applicable”.

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

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• Haemorrhage
Important potential risks	• 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

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the mentioned safety concerns.

In addition, MAH has proposed specific adverse reaction follow-up questionnaires for liver-related adverse events, and renal impairment/renal failure.

Purpose: For collection and reporting of safety information while use of Rivaroxaban Accord.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not Applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Haemorrhage	Section 4.2, 4.3, 4.4, 4.6, 4.8, 4.9 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Important Potential Risks	
Embryo-fetal toxicity	Section 4.3, 4.6, and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Missing information	
Patients with severe renal impairment (CrCl < 30 mL/min)	Section 4.2, 4.4 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
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)	Section 4.5 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Remedial pro-coagulant therapy for excessive haemorrhage	Section 4.9 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Pregnant or breast-feeding women	Section 4.3, 4.6 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this

Safety concern	Routine risk minimisation activities
	safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Section 4.4 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Section 4.2, 4.3 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes
Patients < 18 years	Section 4.2 and 5.2 of Rivaroxaban SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes

V.2. Additional Risk Minimisation Measures

Additional Risk Minimisation Measures have been proposed for important identified risk "haemorrhage" as per reference medicinal product Xarleto® (Rivaroxaban);

Proposed additional risk minimisation measures are listed below and are detailed summarised in **Annexure-6**.

Educational material for prescribers (Prescriber guide and Prescribing information)

Objectives:

To increase an awareness of healthcare professionals regarding risk of haemorrhage with use of Rivaroxaban.

Rationale for the additional risk minimisation activity:

To minimize the reporting frequency of ADR related with this risk by increasing an awareness of healthcare professionals.

Target audience and planned distribution path:

Physician and other healthcare professionals who may prescribe rivaroxaban post approval of this MA application. MAH may distribute 'Prescriber guide and Prescribing information' to above mentioned target audience as per national requirement.

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

Routine pharmacovigilance including analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of the educational material for prescribers will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Patient alert cards

Objectives:

To increase an awareness of healthcare professionals and patients regarding risk of haemorrhage with use of Rivaroxaban.

Rationale for the additional risk minimisation activity:

To minimize the reporting frequency of ADR related with haemorrhage risk by increasing an awareness of healthcare professionals and patients.

Target audience and planned distribution path:

Patients or care taker of patients post approval of this MA application. MAH may distribute 'Patient alert cards" to above mentioned target audience as per national requirement.

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

Routine pharmacovigilance including analysis of ADR reports to assess compliance with SmPC recommendations will allow assessing and judging the success of the risk minimisation measures. Effectiveness of the programme will be analysed by MAH as per the requirements for submission of periodic safety update reports (PSUR) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

V.3 Summary of risk minimisation measures

Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Haemorrhage	Routine risk minimisation measures: Section 4.2, 4.3, 4.4, 4.6, 4.8, 4.9 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: • Educational material for prescribers • Patient alert cards	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Important Potential Risks		
Embryo-fetal toxicity	Routine risk minimisation measures: Section 4.3, 4.6, and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Missing information		
Patients with severe renal impairment (CrCl < 30	Routine risk minimisation measures:	Routine pharmacovigilance activity:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
mL/min)	Section 4.2, 4.4 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific adverse reaction follow-up questionnaires have been proposed for renal impairment/renal failure Additional pharmacovigilance activity: None
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)	Routine risk minimisation measures: Section 4.5 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Remedial pro-coagulant therapy for excessive haemorrhage	Routine risk minimisation measures: Section 4.9 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures:	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None	
Pregnant or breast-feeding women	Routine risk minimisation measures: Section 4.3, 4.6 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Patients with atrial fibrillation (AF) and a prosthetic heart valve	Routine risk minimisation measures: Section 4.4 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting	Routine risk minimisation measures: Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Patients with significant liver diseases (severe hepatic impairment/Child Pugh C)	Routine risk minimisation measures: Section 4.2, 4.3 and 5.2 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific adverse reaction follow-up questionnaires have been proposed for liver-related adverse events. Additional pharmacovigilance activity: None
Patients < 18 years	Routine risk minimisation measures: Section 4.2 and 5.2 of Rivaroxaban SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) (Rivaroxaban)

This is a summary of the risk management plan (RMP) for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg). The RMP details important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), how these risks can be minimised, and how more information will be obtained about Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s risks and uncertainties (missing information).

Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) should be used.

This summary of the RMP for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s RMP.

I. The medicine and what it is used for

Rivaroxaban Accord 2.5 mg film coated tablets co administered with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Rivaroxaban Accord, 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 Accord 10 mg film coated tablets is used 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 Accord 15 mg and 20 mg film coated tablets are used 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.

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

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

Important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), together with measures to minimise such risks and the proposed studies for learning more about Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg)'s risks, are outlined below.

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

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

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

In the case of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg), these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment and signal management activity, 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 Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg). 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);

Important identified risks	• Haemorrhage
Important potential risks	• 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

II.B Summary of important risks

Important Identified Risks: **Haemorrhage**	
Risk minimisation measures	Routine risk minimisation measures: Section 4.2, 4.3, 4.4, 4.6 4.8, 4.9 and 5.3 of Rivaroxaban SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Limited pack sizes Additional risk minimisation measures: • Educational material for prescribers • Patient alert cards

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 Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).

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

There are no studies required for Rivaroxaban Accord film coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).

Part VII: Annexes

Annex 1 – EudraVigilance Interface

To be submitted within 30 days of the commission decision date.

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

MAH has proposed specific adverse reaction follow-up questionnaires for liver-related adverseevents and renal impairment/renal failure.

Targeted Follow-Up Questionnaires for liver-related adverse events

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

Medical History and Risk factors			
1	Any known history of liver, pancreatic and/or biliary abnormalities?	Yes ☐ No ☐	If Yes, specify abnormality(ies) and date (s) of diagnosis
2	Any known history of heart failure and/or hypotension?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
3	Any known underlying viral hepatitis?	Yes ☐ No ☐	If Yes, specify type /genotype and date(s) of diagnosis
4	Any known active malignancy, liver metastasis, fatty liver, liver cirrhosis/fibrosis with Child-Pugh?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
5	How much amount of alcohol consumed by the patient, if any history regarding alcoholism??	Yes ☐ No ☐	If Yes, specify
6	Any known history of genetic diseases that could affect the liver?	Yes ☐ No ☐	If Yes, specify
7	Any known inherited diseases?	Yes ☐ No ☐	If Yes, specify
8	Any known history renal function abnormality?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
9	Any known history of diabetes mellitus?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis

10	Any known hepatitis vaccination?	Yes ☐ No ☐	If Yes, specify and date(s) of vaccination
11	Any known history of autoimmune disease?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
12	Any known history of surgery?	Yes ☐ No ☐	If Yes, specify and date(s) of surgery
13	Any known Use of mentioned medication?	Paracetamol/Acetaminophen ☐ Halothane ☐ Methotrexate ☐ Amiodarone ☐ Antibiotics ☐ NSAIDs ☐ Herbal substances ☐ Cancer therapy ☐	If Yes, specify including dose used and start date
14	Any known current or recent viral infection (i.e; Herpes simplex virus, cytomegalo virus, varicella Toxoplasmosis)?	Yes ☐ No ☐	If Yes, specify
15	Where there other known concomitant medications, including non-prescription drugs, herbal and dietary supplements, used?	Yes ☐ No ☐	If Yes, specify including doses used:

Event Details			
1	Any known clinical evidence of liver failure -altered mental status, coagulopathy/bleeding, jaundice or anemia?	Yes ☐ No ☐	If Yes, specify
2	Any known signs/symptoms related to liver disorder, such as liver enlargement, fatigue, malaise, anorexia, pruritus, abdominal pain, fever or eosinophilia?	Yes ☐ No ☐	If Yes, specify
3	What was the time course of liver injury signs/symptoms?	Kindly elaborate signs/symptoms	
4	Do you consider the reaction to be serious?	Yes ☐ No ☐	If Yes, Define the Reason for Seriousness Patient Died ☐ Involved/Prolonged Hospitalisation ☐ Life Threatening ☐ Disability/Incapacity ☐ Congenital Abnormality ☐ Medically Significant ☐
5	Action Taken with suspect product?	Dose Decreased ☐ Dose Increased ☐ Drug withdrawn ☐	

		Dose not changed ☐ Unknown ☐	
6	Did the event resolve after suspect product was withdrawn?	Yes ☐ No ☐ Unknown ☐	If Yes, provide the details
7	Treatment of event	Yes ☐ No ☐ Unknown ☐	If Yes, provide the details
8	Did patient recover from this event?	Yes ☐ No ☐ Unknown ☐	If available, provide the details of event outcome (s) with date(s) (e.g; Recovered, Not Recovered, Recovered with Sequel, Recovering, Fatal)
9	After the event, was the patient given the suspect product again?	Yes ☐ No ☐	If Yes, provide details of re-exposure and outcome: [rechall_start_date] [rechall_stop_date] [rechall_outcome]

Lab/Diagnostic Data: Please provide laboratory data for before treatment (baseline) and during therapy. In lieu of completing of this section, please provide the supportive documentation (e.g: laboratory test results, liver imaging studies, liver biopsy results, etc.), if available

No	**Test (s)**	**Date (s)**	**Results**
1	ALT, AST, Bilirubin (Total, direct and indirect, conjugated), Gamma-GT, LDH and alkaline phosphatase		
2	Albumin level		
3	PT/PTT/INR		
4	Cholinesterase (CHE)		
5	Eosinophils		
6	complete blood count		
7	Creatinine		
8	Alpha-fetoprotein		
9	Amylase		
10	lipase		
11	Hepatitis and any other serology test results (hepatitis A, B, C, D or E, CMV, EBV, Adenovirus, Coxsackie, Herpes simplex virus, Brucellosis, Leptospirosis and Toxoplasmosis)		
12	CRP		
13	ESR		
14	ANA		
15	Result of liver imaging (ultrasound, CT, MRI, X-ray, etc)		
16	Liver biopsy results, if performed		
17	Additional information, including relevant details of		

	physical examination findings:		

Enclosed documentation: List documents attached and included	
Lab test results	**Specify:**
Liver imaging studies	**Specify:**
Liver biopsy results	**Specify:**
Other	**Specify:**

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

ADDITIONAL INFORMATION FOR LIVER-RELATED ADVERSE EVENTS:

1. What is the therapy duration and administered dosage of rivaroxaban before onset of liver injury?

   _____

   _____

2. .Has patient been switched to rivaroxaban from other anticoagulant recently? If yes, kindly provide details.

   _____

   _____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date
Postal Address: Postcode:	Email:		Tel No.

Targeted Follow-Up Questionnaires for renal impairment/renal failure

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

Medical History and Risk factors			
1	Any known history of renal disorder?	Yes ☐ No ☐	If Yes, specify abnormality(ies) and date (s) of diagnosis
2	Any known history of hypertension, diabetes, heart failure, hypothyroidism, nephrotic syndrome?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
3	Any known underlying infection?	Yes ☐ No ☐	If Yes, specify type /genotype and date(s) of diagnosis
4	Any known history of glomerulonephritis or interstitial nephritis?	Yes ☐ No ☐	If Yes, specify and date(s) of diagnosis
5	Any known alcohol use?	Yes ☐ No ☐	If Yes, specify
6	Any known history of autoimmune disease?	Yes ☐ No ☐	If Yes, specify
7	Any known history of active malignancy or renal tumour?	Yes ☐ No ☐	If Yes, specify and date(s)
8	Any known history of surgery?	Yes ☐ No ☐	If Yes, specify and date(s) of surgery
9	Any known use of Mentioned medication?	NSAIDs ☐ ACE inhibitors ☐	If Yes, specify including dose used and start date

		Contrast agents ☐ Antibiotics ☐ Herbal substances ☐ Cancer therapy ☐	

Event Details			
1	Any known clinical evidence of renal abnormalities OR renal failure like Decreased urine output, Fluid retention, breathlessness, swelling of legs or ankles swelling, etc?	Yes ☐ No ☐	If Yes, specify
2	What was the time course of renal injury signs/symptoms?	Kindly elaborate signs/symptoms.	
3	Do you consider the reaction to be serious?	Yes ☐ No ☐	If Yes, Define the Reason for Seriousness Patient Died ☐ Involved/Prolonged Hospitalisation ☐ Life Threatening ☐ Disability/Incapacity ☐ Congenital Abnormality ☐ Medically Significant ☐
4	Action taken with suspect product?	Dose Decreased ☐ Dose Increased ☐ Drug withdrawn ☐ Dose not changed ☐ Unknown ☐	
5	Did the event resolve after suspect product was withdrawn?	Yes ☐ No ☐ Unknown ☐	If Yes, provide the details
6	Treatment of event	Yes ☐ No ☐ Unknown ☐	If Yes, provide the details
7	Did patient recover from this event?	Yes ☐ No ☐ Unknown ☐	If available, provide the details of event outcome (s) with date(s) (e.g; Recovered, Not Recovered, Recovered with Sequel, Recovering, Fatal)
8	After the event, was the patient given the suspect product again?	Yes ☐ No ☐	If Yes, provide details of re-exposure and outcome: [rechall_start_date] [rechall_stop_date] [rechall_outcome]

Lab/Diagnostic Data: Please provide laboratory data for before treatment (baseline) and during the therapy. In lieu of completing of this section, please provide the supportive documentation (e.g: laboratory test results, renal imaging studies,

etc.), if available			
No	**Test (s)**	**Date (s)**	**Results**
1	Serum creatinine		
2	Glomerular Filtration Rate (eGFR)		
3	Blood Urea		
4	Blood potassium, sodium, phosphate, calcium		
5	Albumin		
6	CRP		
7	leukocytes		
8	LDH/HbdH		
9	Blood gas analysis with pH, bicarbonate and oxygen		
10	Urinary analysis/sediment including proteinuria, hematuria, leukocyturia, dismorph erythrocytes, casts		
11	Any Antibodies Test performed		
12	Urinary or serum eosinophils		

Enclosed documentation: List documents attached and included	
Lab test results	**Specify:**
Renal imaging studies	**Specify:**
Renal biopsy results	**Specify:**
Other	**Specify:**

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	**Route of Admin**	**Daily Dosage**	**Indication**	**Date Started**	**Date Stopped**
1.					
2.					
3.					

ADDITIONAL INFORMATION FOR RENAL IMPAIRMENT/RENAL FAILURE:

1. What is the therapy duration and administered dosage of rivaroxaban before onset of renal injury?

   _____

   _____

2. Has patient been switched to rivaroxaban from other anticoagulant recently? If yes, kindly provide details.

   _____

   _____

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

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

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Educational material for prescribers

▼Rivaroxaban Prescriber Guide

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

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

It includes the following information:

- Dosing recommendations
- Oral intake
- Perioperative management
- Contraindications
- Overdose
- How to manage bleeding complications
- Coagulation testing

Rivaroxaban patient alert card

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

- Treatment compliance
- Taking medication with food (for 15 mg and 20 mg only)
- Recognising signs or symptoms of bleeding
- When to seek medical attention

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

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

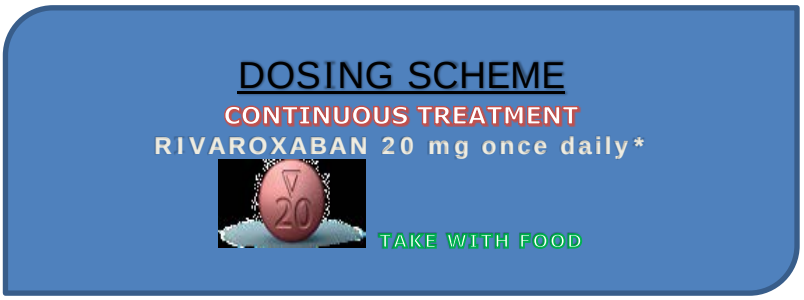
CONTENTS

1. USE IN NON-VALVULAR AF

Prevention of stroke and systemic embolism in adultpatients 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.

DOSING RECOMMENDATIONS

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



* In patients with moderate or severe renal impairment the recommended dose is 15 mg once daily

Patients with renal impairment:

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (15-29 ml/ min) renal impairment the recommended dose is 15 mg once daily. rivaroxaban is to be used with caution in patients with severe renal impairment as limited clinical data indicates a significantly increased plasma concentration. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Duration of therapy:

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

Missed dose:

If a dose is missed the patient should take Rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Patients with non-valvular atrial fibrillation undergoing PCI with stent placement:

There is limited experience of a reduced dose of 15 mg Rivaroxaban once daily (or 10 mg Rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement.

Patients undergoing cardioversion:

Rivaroxaban can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.

ORAL INTAKE

Rivaroxaban 15 mg and 20 mg must be taken with food. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability. For patients who are unable to swallow whole tablets, a Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food. The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 15/20 mg should be stopped at least 24 hours before the intervention if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban should be assessed against the urgency of the intervention.

Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

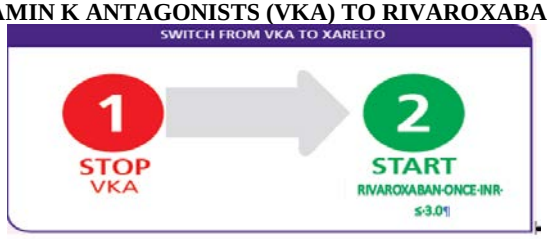
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 20 mg Rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the placement or removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of Rivaroxaban (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the Rivaroxaban dose is administered.

If traumatic puncture occurs the administration of Rivaroxaban is to be delayed for 24 hours.

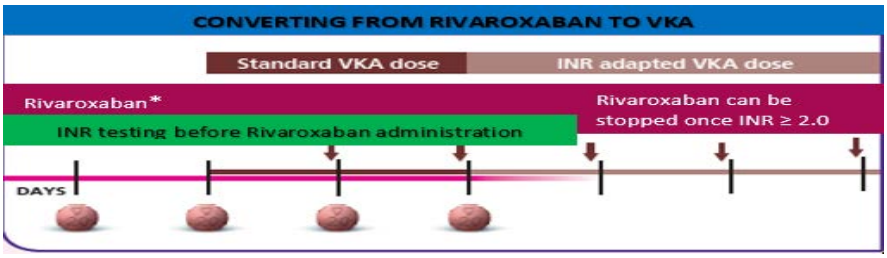
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



For patients treated for **prevention of stroke and systemic embolism,** treatment with VKA should be stopped and Rivaroxaban therapy should be initiated when the **INR is ≤ 3.0.**

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used for this purpose. Treatment with Rivaroxaban only does not require routine coagulation monitoring.

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy. When converting to VKA, Rivaroxaban and VKA should overlap until the **INR is ≥ 2.0**. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban. While patients are on both Rivaroxaban and VKA the **INR should be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban should be started at the time of discontinuation

- Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start Rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral drug

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS
The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban may increase the risk of bleeding. Therefore Rivaroxaban is contraindicated in patients:

- With clinically significant active bleeding
- With a lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux,etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban
- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS

Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications.
Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding:

- ***Patients with renal impairment:*** See “dosing recommendations” section for patients with renal impairment

- ***Patients concomitantly receiving other medicinal products:***

    - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
    - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- ***Patients with other haemorrhagic risk factors:***
  As with other antithrombotics, Rivaroxaban is not recommended in patients with an increased bleeding risk such as:
    - congenital or acquired bleeding disorders
    - uncontrolled severe arterial hypertension
    - other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
    - vascular retinopathy
    - bronchiectasis or history of pulmonary bleeding

- ***Patients with prosthetic valves:***

Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

OVERDOSE

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

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving Rivaroxaban, the next Rivaroxaban administration should be delayed, or treatment discontinued as appropriate.

Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving Rivaroxaban. Due to the high plasma protein binding Rivaroxaban is not expected to be dialysable.

COAGULATION TESTING

Rivaroxaban does not require routine coagulation monitoring. However, measuring Rivaroxaban levels may be useful in exceptional situations where knowledge of Rivaroxaban exposure may help to make clinical decisions, e.g. overdose and emergency surgery.

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

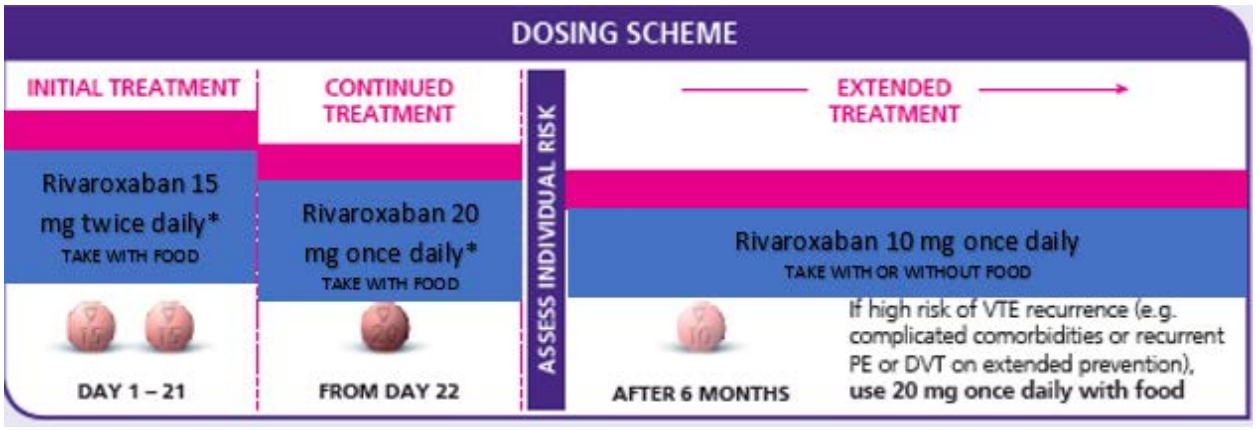
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity of Rivaroxaban. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban to VKA as described above.

2. TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE

Treatment of DVT and PE and prevention of recurrent DVT and PE in adults (not recommended for use in haemodynamically unstable PE patients).

DOSING RECOMMENDATIONS

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



* Patients with DVT/PE and renal impairment may be considered for dose reduction.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg **once daily**. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban 10 mg **once daily**, a dose of Rivaroxaban 20 mg **once daily** should be considered.

Rivaroxaban 10 mg is **not** recommended for the initial 6 months treatment of DVT or PE.

Patients with renal impairment:

Rivaroxaban is to be used with caution in patients with severe renal impairment and is not recommended in patients with creatinine clearance <15 ml/min. Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients.

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

However, during the continued treatment phase, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Duration of therapy:

The duration of therapy should be individualised after assessment of the treatment benefit against the risk for bleeding. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Missed dose:

- **Twice daily treatment period** (15 mg bid for the first three weeks): If a dose is missed, the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. Continue with the regular 15 mg twice daily intake on the following day
- **Once daily treatment period** (beyond three weeks): If a dose is missed, the patient should take Rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

ORAL INTAKE

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

For patients who are unable to swallow whole tablets, a Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 15/20 mg should be stopped at least 24 hours before the intervention if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician.

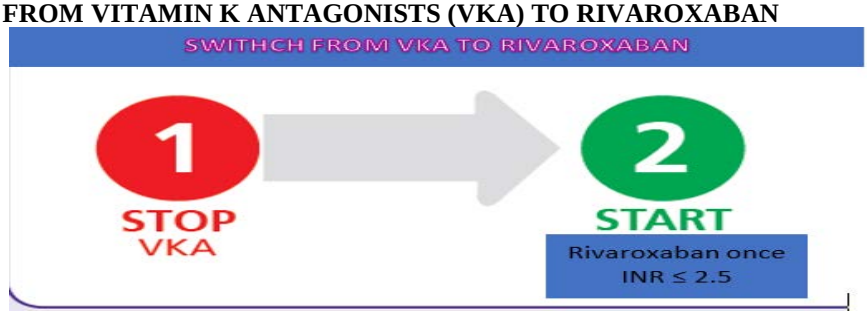
SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- post-operative use of indwelling epidural catheters;
- concomitant use of medicinal products affecting haemostasis;
- traumatic or repeated epidural or spinal puncture.

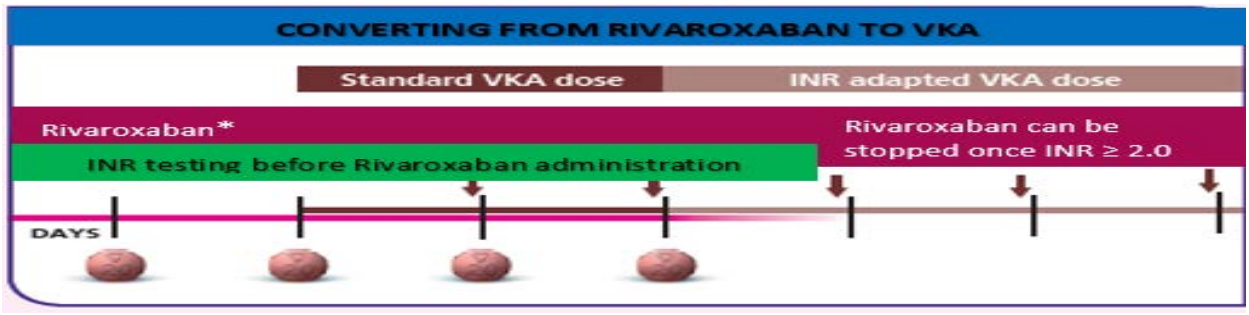
Patients must be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg or 20 mg Rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. For the placement/removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of Rivaroxaban (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban dose is administered.
If traumatic puncture occurs the administration of Rivaroxaban is to be delayed for 24 hours.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



For patients treated for **DVT, PE and prevention of recurrent DVT and PE**, treatment with VKA should be stopped and Rivaroxaban therapy should be initiated when the **INR is ≤ 2.5**.
INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used for this purpose. Treatment with Rivaroxaban only does not require routine coagulation monitoring.

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.
When converting to VKA, Rivaroxaban and VKA should overlap until the **INR is ≥ 2.0**. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban. While patients are on both Rivaroxaban and VKA the **INR should be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban should be started at the time of discontinuation.
- Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start Rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS
The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban may increase the risk of bleeding. Therefore Rivaroxaban is contraindicated in patients:

- With clinically significant active bleeding
- With a lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban
- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS
Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding:

- ***Patients with renal impairment:*** See "dosing recommendations" section for patients with renal impairment
- ***Patients concomitantly receiving other medicinal products:***
    - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
    - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- ***Patients with other haemorrhagic risk factors:***
  As with other antithrombotics, Rivaroxaban is not recommended in patients with an increased bleeding risk such as:
    - congenital or acquired bleeding disorders
    - uncontrolled severe arterial hypertension
    - other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
    - vascular retinopathy

- bronchiectasis or history of pulmonary bleeding.

- ***Patients with prosthetic valves:***
  Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

OVERDOSE

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

HOW TO MANAGE BLEEDING COMPLICATIONS

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

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving Rivaroxaban. Due to the high plasma protein binding Rivaroxaban is not expected to be dialyzable

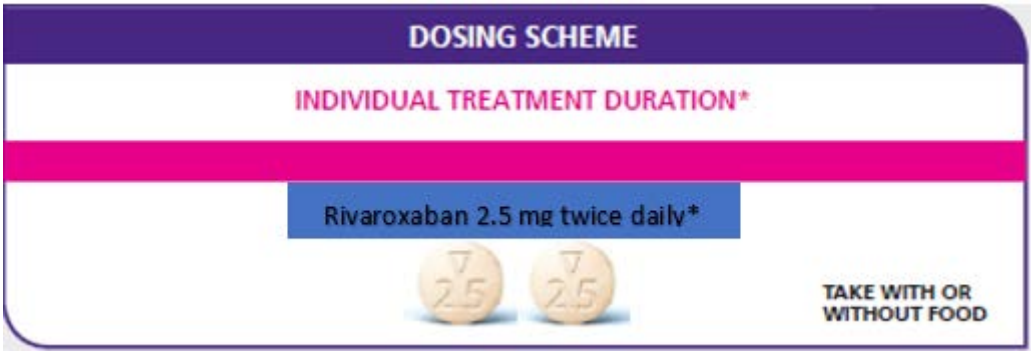
COAGULATION TESTING

Rivaroxaban does not require routine coagulation monitoring. However, measuring Rivaroxaban levels may be useful in exceptional situations where knowledge of Rivaroxaban exposure may help to make clinical decisions, e.g. overdose and emergency surgery.
Anti-FXa assays with Rivaroxaban specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated haemostatic status can also be assessed by PT using Neoplastin as described in the SmPC.
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity of Rivaroxaban. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban to VKA as described above.

3. USE IN ACSsp (ACUTE CORONARY SYNDROME SECONDARY PREVENTION)

Prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine.

DOSING RECOMMENDATIONS



* Treatment should be regularly evaluated in the individual patient weighing the risk for the ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited

The recommended dose of Rivaroxaban is 2.5 mg **twice daily**, starting as soon as possible after stabilisation of the index ACS event but at the earliest 24 hours after hospital admission and at the time when parenteral anticoagulation therapy would normally be discontinued.

In addition to Rivaroxaban 2.5 mg, patients should also take a daily dose of 75-100 mg ASA or a daily dose of 75-100 mg ASA in addition to a standard daily dose of ticlopidine.

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

Patients with renal impairment:

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 ml/min), as limited clinical data indicates a significantly increased plasma concentration, consequently increasing bleeding risk. Use is not recommended in patients with creatinine clearance <15 ml/min. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 ml/min) or moderate renal impairment (creatinine clearance 30-49 ml/min).

In patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Rivaroxaban is to be used with caution.

Duration of therapy:

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.

Missed dose:

If a dose is missed the patient should continue with the regular 2.5 mg Rivaroxaban dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

ORAL INTAKE

Rivaroxaban 2.5 mg can be taken with or without food. For patients who are unable to swallow whole tablets, a Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube.

The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 2.5 mg should be stopped at least 12 hours before the intervention if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban should be assessed against the urgency of the intervention.

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- post-operative use of indwelling epidural catheters

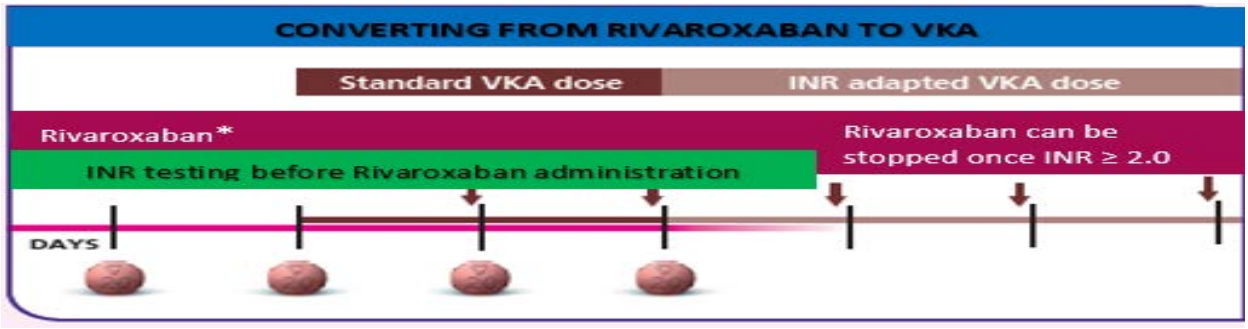
- concomitant use of medicinal products affecting haemostasis
- traumatic or repeated epidural or spinal puncture

Patients must be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.
There is no clinical experience with the use of 2.5 mg Rivaroxaban with ASA alone or with ASA plus ticlopidine in these situations. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used for this purpose. Treatment with Rivaroxaban only does not require routine coagulation monitoring.

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose
It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.
When converting to VKA, Rivaroxaban and VKA should overlap until the **INR is ≥ 2.0**. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.
INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban. While patients are on both Rivaroxaban and VKA the **INR should be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban should be started at the time of discontinuation
- Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start Rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS
The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS
Like all anticoagulants, Rivaroxaban may increase the risk of bleeding. Therefore Rivaroxaban is contraindicated in patients:

- With clinically significant active bleeding
- With a lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients
- With ACS who had a prior stroke or a transient ischaemic attack (TIA) and are receiving antiplatelet therapy

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban
- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS

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

Use in these patients should be balanced against the benefit in terms of prevention of atherothrombotic events. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

- ***Patients with renal impairment:*** See "dosing recommendations" section for patients with renal impairment
- ***Patients concomitantly receiving other medicinal products:***
    - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
    - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
    - After an acute coronary syndrome patient on treatment with Rivaroxaban and ASA or Rivaroxaban and ASA plus ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- ***Patients with other haemorrhagic risk factors:***

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

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

- ***Patients with prosthetic valves:***

Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

- ***Rivaroxaban should be used with caution in ACS patients:***
    - >75 years of age if co-administered with ASA alone or with ASA plus ticlopidine
    - with a low weight (<60 kg) if co-administered with ASA alone or with ASA plus ticlopidine

OVERDOSE

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

HOW TO MANAGE BLEEDING COMPLICATIONS

Should bleeding complications arise in a patient receiving Rivaroxaban, the next Rivaroxaban administration should be delayed or treatment discontinued as appropriate.

Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement and haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving Rivaroxaban. Due to the high plasma protein binding Rivaroxaban is not expected to be dialysable.

COAGULATION TESTING

Rivaroxaban does not require routine coagulation monitoring. However, measuring Rivaroxaban levels may be useful in exceptional situations where knowledge of Rivaroxaban exposure may help to make clinical decisions, e.g. overdose and emergency surgery.

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

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity of Rivaroxaban. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban to VKA as described above.

4. PREVENTION OF VTE IN ADULT PATIENTS UNDERGOING ELECTIVE HIP OR KNEE REPLACEMENT SURGERY

DOSING RECOMMENDATIONS

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.

Patients with renal impairment:
Rivaroxaban is to be used with caution in patients with severe (creatinine clearance 15 - 29 ml/min) renal impairment. Use is not recommended in patients with creatinine clearance < 15 ml/min (see SmPC sections 4.2 and 5.2).

Patients with mild (creatinine clearance 50-80 ml/min) or moderate (creatinine clearance 30-49 ml/min) renal impairment treated for prevention of VTE in adult patients undergoing elective hip or knee replacement surgery do not require a dose reduction.

Duration of therapy:
The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

Missed dose:
If a dose is missed the patient should take Rivaroxaban immediately and then continue the following day with once daily intake as before. The dose should not be doubled within the same day to make up for a missed dose.

ORAL INTAKE

Rivaroxaban 10 mg can be taken with or without food.

For patients who are unable to swallow whole tablets, a Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 10 mg should be stopped at least 24 hours before the intervention if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE
When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of

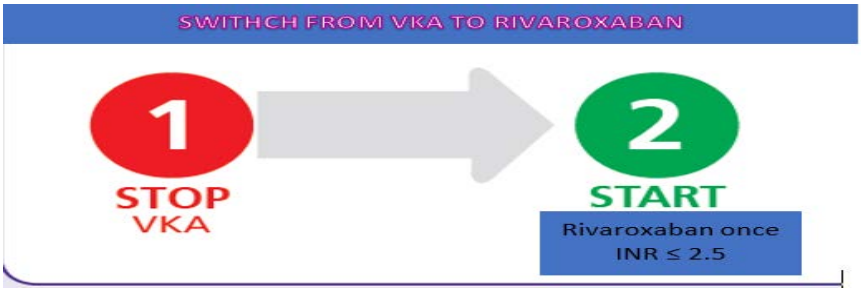
indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the placement or removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours should elapse after the last administration of Rivaroxaban before removal of an epidural catheter (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban dose is administered.

If traumatic puncture occurs the administration of Rivaroxaban is to be delayed for 24 hours.

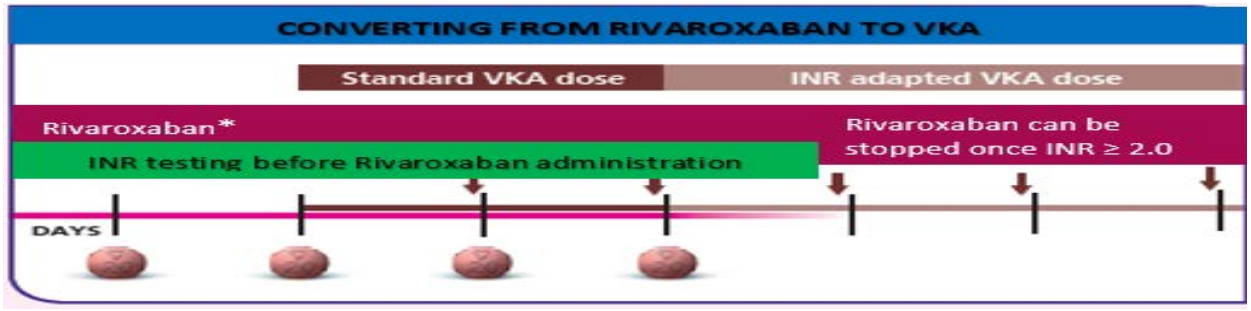
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



For patients treated for **DVT, PE and prevention of recurrent DVT and PE**, treatment with VKA should be stopped and Rivaroxaban therapy should be initiated when the **INR is ≤ 2.5**.

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used for this purpose. Treatment with Rivaroxaban only does not require routine coagulation monitoring.

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy.

When converting to VKA, Rivaroxaban and VKA should overlap until the **INR is ≥ 2.0**. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of Rivaroxaban. While patients are on both Rivaroxaban and VKA the **INR should be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban should be started at the time of discontinuation.

- Patients with parenteral drug on a fixed dosing scheme such as Low Molecular Weight Heparin (LMWH): discontinue parenteral drug and start Rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS
The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban may increase the risk of bleeding. Therefore Rivaroxaban is contraindicated in patients:

- With clinically significant active bleeding
- With a lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban
- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS
Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. In patients receiving Rivaroxaban for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding:

- ***Patients with renal impairment:*** See "dosing recommendations" section for patients with renal impairment
- ***Patients concomitantly receiving other medicinal products:***
  - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
  - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- ***Patients with other haemorrhagic risk factors:***
  As with other antithrombotics, Rivaroxaban is not recommended in patients with an increased bleeding risk such as:
  - congenital or acquired bleeding disorders
  - uncontrolled severe arterial hypertension
  - other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
  - vascular retinopathy
  - bronchiectasis or history of pulmonary bleeding.
- ***Patients with prosthetic valves***
  Safety and efficacy of Rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban is not recommended for these patients.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via email [redacted]

Rivaroxaban 2.5, 10, 15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet.

Indication(s): **2.5mg** Rivaroxaban, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. Rivaroxaban, 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. **10mg** Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **15mg/20mg** Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). Treatment of DVT & PE, & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients).

Posology & method of administration: **2.5mg** – Oral b.i.d. dose; patients should also take a daily dose of 75 – 100 mg ASA or a daily dose of 75 – 100 mg ASA in addition to a standard daily dose of ticlopidine. Start Rivaroxaban as soon as possible after stabilisation, including revascularisation for ACS; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation. If dose is missed take next dose, do not double the dose. **10mg** – hip or knee replacement surgery: Oral o.d. dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. DVT & PE: When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg o.d. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban 10 mg o.d., a dose of Rivaroxaban 20 mg o.d. should be considered. **15mg/20mg** – Take with food. SPAF: 20 mg orally o.d. DVT & PE: 15 mg b.i.d. for 3 weeks followed by 20 mg o.d. for continued treatment & prevention of recurrent DVT & PE. **All strengths** - Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants.

Special populations: Patients undergoing cardioversion: Rivaroxaban can be initiated or continued in patients who may require cardioversion. Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement: There is limited experience of a reduced dose of 15 mg Rivaroxaban once daily (or 10 mg Rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30 – 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation & undergo PCI with stent placement. **Renal impairment:** mild (creatinine clearance 50-80 ml/min) - no dose adjustment; **2.5mg /10mg** - moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. **15mg/20mg –** moderate (creatinine clearance 30-49 ml/min) & severe (creatinine clearance 15-29ml/min) - SPAF: reduce dose to 15mg o.d., DVT & PE: 15 mg b.i.d. for 3 weeks, thereafter 20mg o.d. Consider reduction from 20mg to 15mg o.d. if patient's bleeding risk outweighs risk for recurrent DVT & PE; **All strengths** – Severe

impairment: limited data indicate rivaroxaban concentrations are significantly increased, use with caution. Creatinine clearance <15 ml/min - not recommended. **Hepatic impairment:** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C. **Paediatrics:** Not recommended.

Contra-indications: Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **2.5mg** - concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month.

Warnings & precautions (W&P): Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severechaemorrhage occurs. Increasing age may increase haemorrhagic risk. Rivaroxaban should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions.
Not recommended: in patients with an increased bleeding risk (refer to SmPC); in patients receiving concomitant systemic treatment with strong concurrent CYP3A4- & P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with prosthetic heart valves; **2.5mg** treatment in combination with antiplatelet agents other than ASA & ticlopidine; 10mg/15mg/20mg in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy. Use with caution: in patients with severe renal impairment or with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; treated concomitantly with medicines affecting haemostasis; when neuraxial anaesthesia or spinal/epidural puncture is employed; in patients at risk of ulcerative gastrointestinal disease (prophylactic treatment may be considered); **2.5mg** in ACS patients ≥ 75 years of age or with lower body weight (<60kg). Patients on treatment with Rivaroxaban & ASA or Rivaroxaban & ASA plus ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. **All strengths**- There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Rivaroxaban contains lactose.

Interactions: Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving NSAIDs, ASA or platelet aggregation inhibitors due to the increased bleeding risk; use with caution in patients concomitantly receiving SSRIs/SNRIs due to a possible increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis.

Pregnancy & breast feeding: Contra-indicated.

Effects on ability to drive & use machines: syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines.

Undesirable effects: Common: anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, increase in transaminases, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia very common in women <55 yrs treated for DVT, PE & prevention of recurrence), renal impairment, fever, peripheral oedema, decreased general strength & energy, post-procedural haemorrhage, contusion, wound secretion. Serious: cf. CI/Warnings & Precautions – in addition: thrombocytosis, thrombocytopenia, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome, anaphylactic reactions including shock, angioedema & allergic oedema, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, hepatic impairment, cholestasis & hepatitis (incl. hepatocellular injury), increases in bilirubin, blood alkaline phosphatase & GGT, increased conjugated bilirubin, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention. Prescribers should consult SmPC in relation to full side effect information.

Overdose: No specific antidote is available.

Adverse events should be reported. Reporting forms via email [redacted]

Patient Alert Card

What should I know about Rivaroxaban?

- Rivaroxaban thins the blood, which prevents you from getting dangerous blood clots.
- Rivaroxaban must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, never skip a dose.
- You must not stop taking Rivaroxaban without first talking to your doctor as your risk of blood clots may increase.
- Tell your health care provider about any other medicines you are currently taking, took recently or intend to start taking, before you start Rivaroxaban.
- Tell your health care provider that you are taking Rivaroxaban before any surgery or invasive procedure.

When should I seek advice from my health care provider?

When taking a blood thinner such as Rivaroxaban it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Rivaroxaban if you know you are at risk of bleeding, without first discussing this with your doctor. Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:

- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- blood in your urine which may be pink or brown, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds

How do I take Rivaroxaban?

To ensure optimal protection, Rivaroxaban

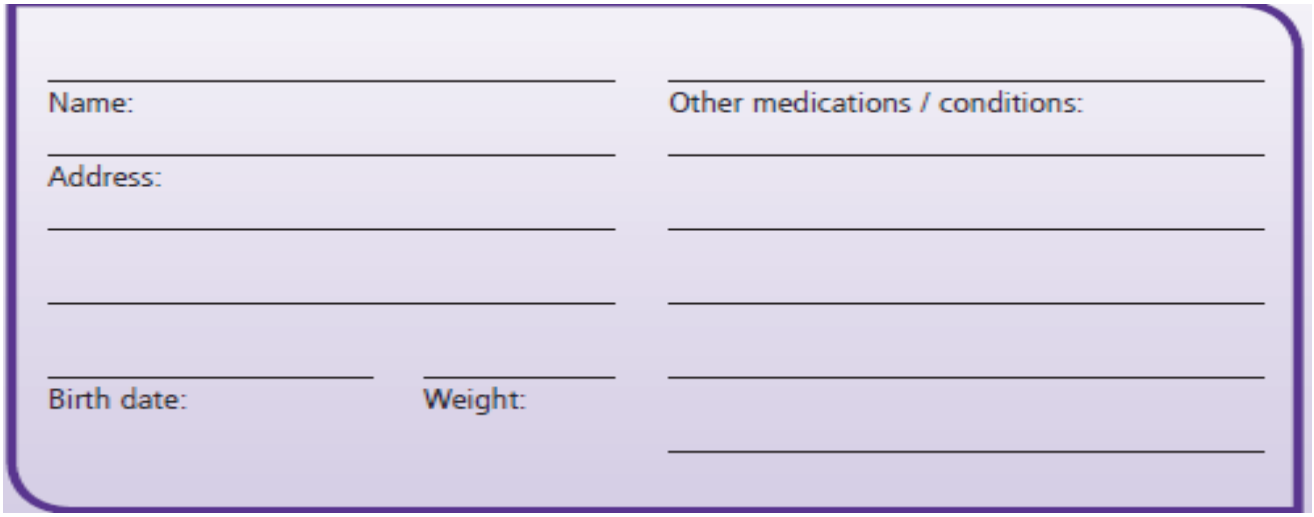
- 2.5 mg can be taken with or without food
- 10 mg can be taken with or without food
- 15 mg must be taken with food
- 20 mg must be taken with food

Keep this card with you at all times

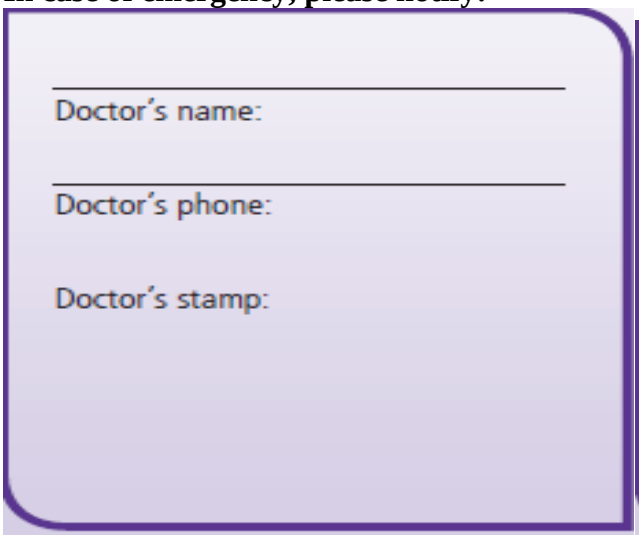
Present this card to every physician or dentist prior to treatment

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the patient information leaflet for how to report side effects.

I am under anticoagulation treatment with Rivaroxaban



In case of emergency, please notify:



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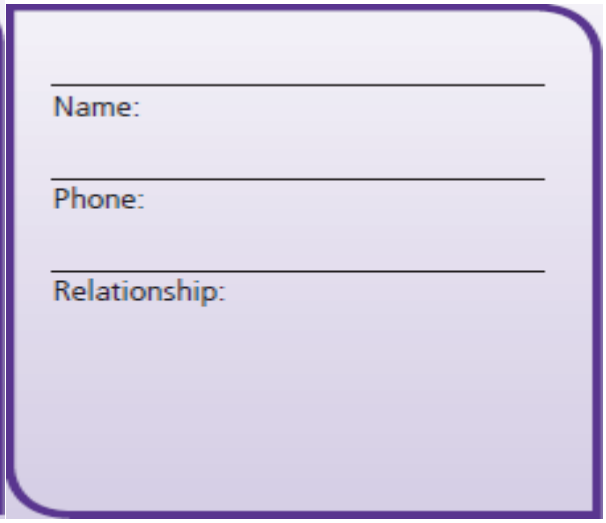

Information for healthcare providers:
INR values should not be used as they are not a dependable measure of the anticoagulant activity of Rivaroxaban.

Annex 7 - Other supporting data (including referenced material)

1. Summary of Product Characteristic (SmPC) and Package Information Leaflet (PIL) of Rivaroxaban Accord film-coated tablets (2.5 mg, 10 mg, 15 mg and 20 mg).
2. Summary of Xarleto® (Rivaroxaban) RMP version 11.4, with data lock point dated 01-Aug-2018.
3. CHMP Day-120 List of Questions of Rivaroxaban Accord (EMEA/H/C/005279) dated 04-Nov-2019.
4. CHMP Day-180 List of Outstanding issues of Rivaroxaban Accord (EMEA/H/C/005279) dated 28-May-2020.
5. CHMP Day 195 Joint Assessment Report received on 08 September 2020

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

Not applicable.