SANDOZ

RIVAROXABAN PRESCRIBER GUIDE

Date of preparation: February 2024

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

- **Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events. when co-administered with acetylsalicylic acid (ASA)**
- **Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers when co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine**

It includes the following information:

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

Prescriber Guide

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

The Prescriber Guide does not substitute the Rivaroxaban Summary of Product Characteristics (SmPC). Before prescribing, please also read the SmPC.*

*https://www.medicines.org.uk/emc

Rivaroxaban patient alert card

A patient alert card is provided with the product package to each patient who is prescribed Rivaroxaban. Please explain the implications of anticoagulant treatment to patients and/or caregiver, in particular highlighting the need for:

- Treatment compliance
- Recognising signs or symptoms of bleeding
- When to seek medical attention
- The need to inform HCPs that they are taking rivaroxaban if they need to have any surgery or invasive procedure

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 or caregiver to carry the patient alert card with them at all times and present it to every healthcare provider. Please also instruct the patient to tick the appropriate box on the patient alert card corresponding to the dose that they are taking.

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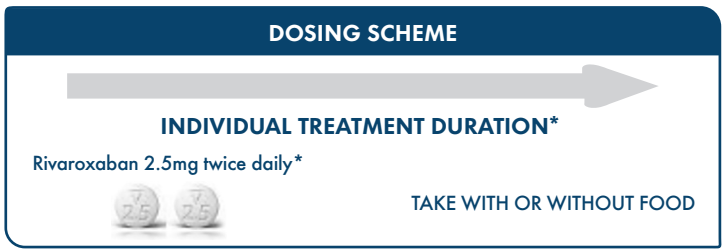
ADULT: USE IN CORONARY ARTERY DISEASE (CAD) AND PERIPHERAL ARTERY DISEASE (PAD)

Prevention of atherthrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events when co-administered with acetylsalicylic acid (ASA)

DOSING RECOMMENDATIONS

Patients taking Rivaroxaban 2.5mg twice daily should also take a daily dose of 75-100mg acetylsalicylic acid (ASA).



* See dosing recommendations for required daily dose

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment periods for all patients.

Treatment should not be started in patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, until haemostasis is achieved (see also section 5.1 of the SmPC).

Co-administration with antiplatelet therapy:

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Rivaroxaban 2.5mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen

Patients with renal impairment:

No dose adjustment is required in patients with mild renal impairment (creatinine clearance 50-80ml/min) or moderate renal impairment (creatinine clearance 30-49ml/ min). Rivaroxaban is to be used with caution in patients with severe renal impairment (CrCl 15-29ml/min) and is not recommended in patients with CrCl <15ml/min.

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

Duration of therapy:

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.

Missed dose:

If a dose is missed, the patient should continue with the regular 2.5mg 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 2.5mg 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 immediately prior to use and then administered orally.

The crushed Rivaroxaban tablet may also be given through a nasogastric or gastric feeding tubes.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 2.5mg 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

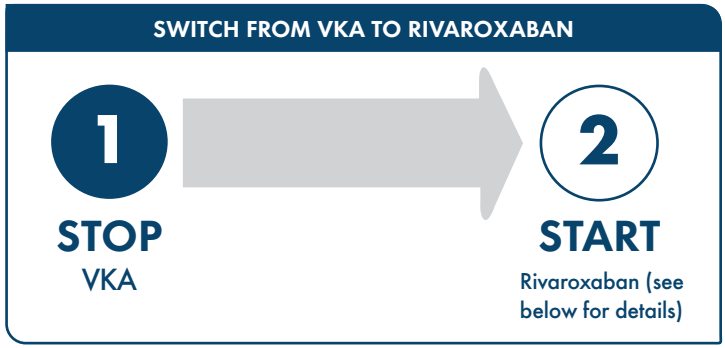
When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- 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.

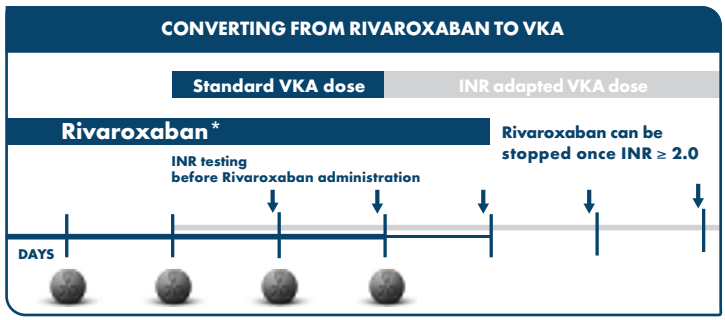
There is no clinical experience with the use of Rivaroxaban 2.5mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information. To reduce the potential risk of bleeding associated with the concurrent use 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.

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 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 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 not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban.** Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose

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

Also concomitant treatment of CAD/PAD with Rivaroxaban 2.5mg and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. Treatment with Rivaroxaban 2.5 mg should be avoided in patients with previous stroke or TIA receiving dual 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

The risk of bleeding increases with increasing age. Several sub-groups of patients are at increased risk of bleeding and should be carefully monitored for signs and symptoms of bleeding complications. Use of rivaroxaban is not recommended for patients with an history of thrombosis who are diagnosed with antiphospholipid syndrome.

Use of Rivaroxaban in combination with dual antiplatelet therapy 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)
  - Patients being treated for CAD or PAD with Rivaroxaban and antiplatelet agents only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
  - The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (For patients with renal impairment see further above)
- **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

- **Patients with cancer:**

  Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease.

  Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during Rivaroxaban therapy.

  In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban is contraindicated.

- **Patients with antiphospholipid syndrome:**
  Use of rivaroxaban is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.

- **Rivaroxaban should be used with caution in CAD/PAD patients:**
  - ≥ 75 years of age if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine. The benefit-risk of the treatment should be individually assessed on a regular basis.
  - with lower body weight (< 60 kg) if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine.
  - CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with rivaroxaban (see SmPC section 5.1).

- **Other warnings and precautions in CAD/PAD patients**
  In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Rivaroxaban 2.5 mg twice daily have been investigated in combination with ASA.

  In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Rivaroxaban 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel (up to 6 months, see also section 5.1 of the SmPC). If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided.

  Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment periods for all patients.

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Rivaroxaban and above. The use of activated charcoal to reduce absorption in case of overdose may be considered. A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available.

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
- If bleeding cannot be controlled with the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa) should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving Rivaroxaban.

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:

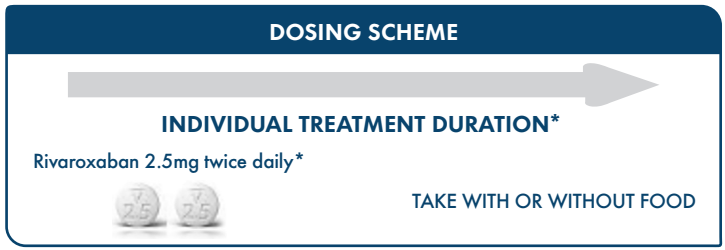
Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR).

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.

ADULT: 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 clopidogrel or 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

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

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment periods for all patients.

The recommended dose of Rivaroxaban is 2.5mg **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.

Patients with renal impairment:

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

In patients with moderate renal impairment (creatinine clearance 30-49ml/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 2.5mg 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 2.5mg 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 immediately prior to use and then administered orally.

The crushed Rivaroxaban tablet may also be given through gastric tubes.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban 2.5mg 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

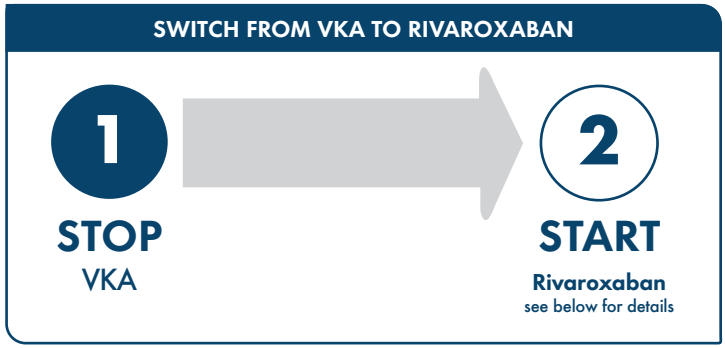
When neuraxial (spinal/epidural) anaesthesia or puncture is employed, patients treated with antithrombotic agents are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk may be increased by:

- 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.

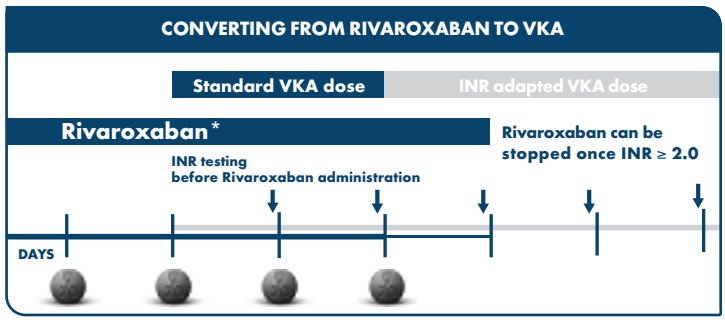
There is no clinical experience with the use of Rivaroxaban 2.5 mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information. To reduce the potential risk of bleeding associated with the concurrent use 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.

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 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 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 not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban.** Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose

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

The risk of bleeding increases with increasing age. 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.

- **Co-administration with antiplatelet therapy:**
  In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Rivaroxaban 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.
- **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 patients treated with Rivaroxaban and antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
  - The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients as described in section 4.5 of the SmPC. (For patients with renal impairment see further above)
- **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

- **Patients with cancer:**
  Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease.

  Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during Rivaroxaban therapy.

  In patients with malignant neoplasms at high risk of bleeding , the use of Rivaroxaban is contraindicated.

- **Other warnings and precautions in ACS patients:**
  In recent ACS patients, efficacy and safety of Rivaroxaban 2.5 mg twice daily have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ ticlopidine.

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

- **Rivaroxaban should be used with caution in ACS patients:**
  Rivaroxaban, co-administered with ASA or with ASA plus clopidogrel or ticlopidine, should be used with caution in ACS patients:
  - ≥75 years of age. The benefit risk of the treatment should be individually assessed on a regular basis
  - With a lower weight (<60 kg)

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Rivaroxaban and above. The use of activated charcoal to reduce absorption in case of overdose may be considered. A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available.

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
- If bleeding cannot be controlled with the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa) should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving Rivaroxaban

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.

DOSING OVERVIEW TABLE

Please consult SmPC for full product information.

INDICATION[1]	DOSING[1]
Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events	**Rivaroxaban 2.5mg twice daily in combination with ASA 75-100mg/day**
Prevention of atherothrombotic events in adult patients **after an ACS** with elevated cardiac biomarkers	**Rivaroxaban 2.5mg twice daily in combination with standard antiplatelet therapy** (ASA 75-100mg/day alone or ASA 75-100mg/day plus clopidogrel 75mg/day or a standard dose of ticlopidine)

For patients who are unable to swallow whole tablets, Rivaroxaban tablets may be crushed and mixed with immediately prior to use and administered orally.

Reference: 1. Rivaroxaban Sandoz 2.5mg Summary of Product Characteristics.

Reporting of adverse events

Adverse events should be reported.

Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Adverse events should also be reported to Sandoz Ltd via adverse.event.uk@sandoz.com or online through the pharmacovigilance intake (PVI) tool at https://pvi1j.solutions.iqvia.com

If you have a question about the product, please contact Medical Information on 01276 698101 or via email at Sandozgb@EU.propharmagroup.com

Further information

Please refer to Rivaroxaban SPCs for full prescribing information which can be found on the Electronic Medicine Compendium website www.medicines.org.uk/emc/

This educational material is provided by Sandoz Ltd and is mandatory as a condition of the marketing authorisation in order to further minimise important selected risks.

NOTES

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