PRESCRIBER GUIDE

Rivaroxaban 10 mg, 15 mg and 20 mg Film-coated tablets

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Contents

Rivaroxaban PharOS

10 mg, 15 mg and 20 mg Film-coated tablets

PRESCRIBER'S GUIDE

Prescriber Guide

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

The prescriber guide does not substitute the Rivaroxaban Summary of Product Characteristics (SmPC).

Patient Alert Card

A patient alert card must be provided to each patient who is prescribed rivaroxaban 10 mg, 15 mg or 20 mg and is provided with the product package. The implications of anticoagulant treatment should be explained. Specifically, the need for compliance, signs of bleeding and when to seek medical attention should be discussed with the patient.

The patient alert card will inform physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider.

Dosing Recommendations

Stroke prevention in adult patients with non-valvular atrial fibrillation

The recommended dose 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 ischemic attack (SPAF) is 20 mg once daily.

DOSING SCHEME

Continuous treatment **Take with food**

Rivaroxaban 20mg once daily*

*Recommended dosing scheme for patients with atrial fibrillation and moderate or severe renal impairment see following text.

Patients with renal impairment

In patients with moderate (creatinine clearance [CrCl] 30–49 ml/min) or severe (CrCl 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 (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <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.

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 undergoing Percutaneous Coronary Intervention (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 [CrCl 30-49 ml/min]) in addition of 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:

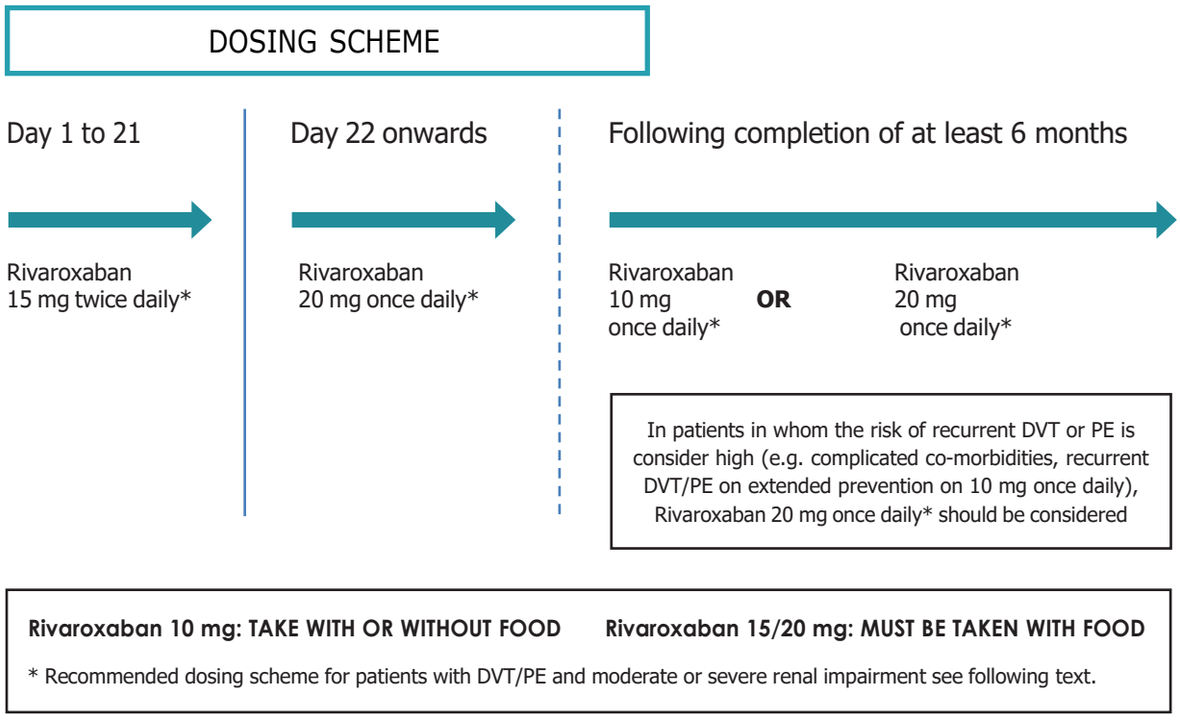
Rivaroxaban can be initiated or continued in patients who may require cardioversion.

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. For all patients, confirmation should be sought prior to cardioversion that the patient has taken rivaroxaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and prevention of recurrent DVT and PE in adult patients.

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

Patients with moderate (CrCl 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairmenttreated for acute DVT, acute PE and prevention of recurrent DVT and PE should be treated with rivaroxaban 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is rivaroxaban 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed riskfor bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modeling and has not been studied in this clini- cal setting. Rivaroxaban is to be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min) and is not recommended in patients with creatinine clearance < 15 ml/ min. When the recommended dose is 10 mg once daily, (after ≥6 months of therapy) 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

Short duration of therapy (≥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/PE, or a history of recurrent DVT/PE.

Missed dose

Twice daily treatment period (15 mg twice for the first 3 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 3 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.

Prevention of VTE in adult patient 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 hemostasis has been established.

Duration of treatment

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopedic 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.

Oral Intake

Rivaroxaban 10 mg can be taken with or without food.

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 15mg or 20mg 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, if possible and based on the clinical judgement of the physician:

• Rivaroxaban 10/15/20 mg should be stopped at least 24 hours before the intervention

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

Spinal/epidural anesthesia or puncture

When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma 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 hemostasis. 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. numbnessor 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.

For indication specific recommendations please refer to the sections below:

• Prevention of stroke and systemic embolism in adult patients with adult patients with NVAF

• Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients

There is no clinical experience with the use of 10/15/20 mg rivaroxaban in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia 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 and should be weighed against the urgency of the diagnostic procedure.

For the 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 adult 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.

• Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

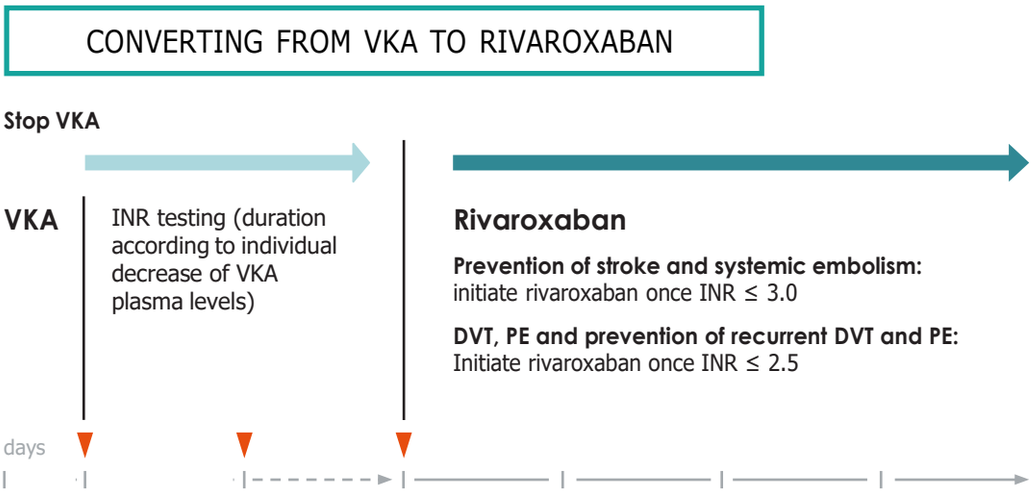
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2 of the SmPC).

At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. 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.

- Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischemic events
- Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers

Converting from VKA to Rivaroxaban



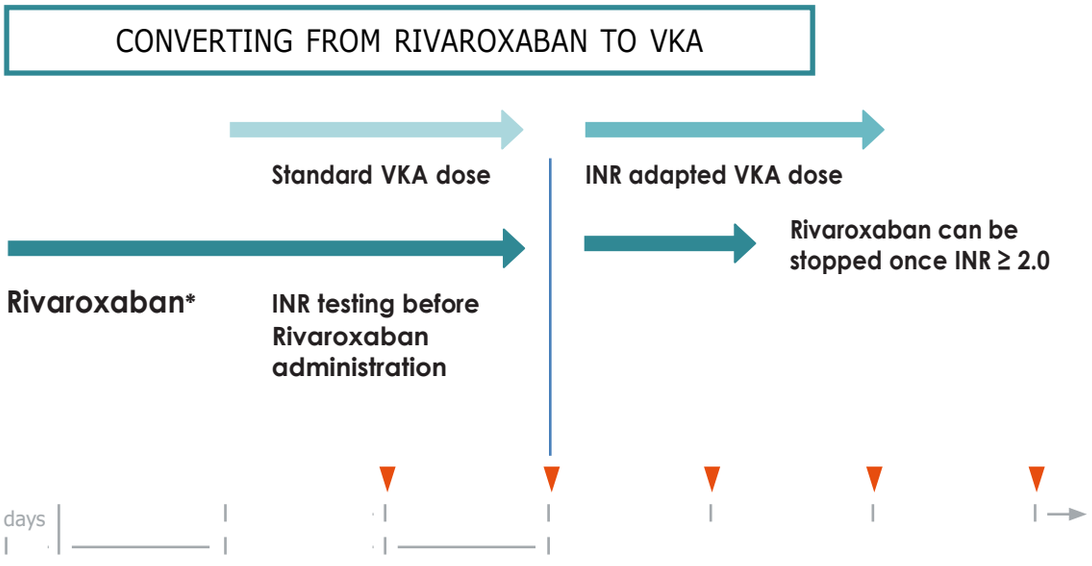
*See dosing recommendations for required daily dose

For patients treated for **prevention of stroke and systemic embolism**, treatment with Vitamin K Antagonists (VKA) should be stopped and rivaroxaban therapy should be initiated when the **INR is ≤ 3.0**.

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 coagulation monitoring.

Converting from Rivaroxaban to VKA



*See dosing recommendations for required daily dose

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

When converting to VKA, rivaroxaban and VKA should be given overlapping until the INR ≥ 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 values obtained at least 24 hours after the last dose reliably reflect the VKA dosing.

Converting from Parenteral Anticoagulants to rivaroxaban

- 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.
- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Start rivaroxaban at the time of discontinuation.

Converting from rivaroxaban to Parenteral Anticoagulants

Give the first dose of the parenteral anticoagulant at the time that the next rivaroxaban dose would be taken.

Populations Potentially at Higher Risk of Bleeding

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 hemorrhage, known or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- receiving concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), LMWHs (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban etc.) except under the circumstances of switching anticoagulant therapy 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
- concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischemic attack (TIA).
- concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month.
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The risk of bleeding increases with increasing age.

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

Treatment decision in these patients should be carried out after assessment of treatment benefit against the risk for bleeding.

Patients with renal impairment

See "dosing recommendations" for patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 - 29 ml/min) renal impairment. Rivaroxaban is to be used with caution in patients with creatinine clearance (15-29 ml/min) and in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. Use of rivaroxaban is not recommended in patients with creatinine clearance <15 ml/min.

Patients concomitantly receiving other medicinal products

- Systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): use of rivaroxaban is not recommended
- Care is to be taken in patients concomitantly receiving drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA) or platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
- ACS patients and CAD/PAD patients: Patients on treatment with rivaroxaban and ASA or rivaroxaban and ASA plus clopidogrel/ticlopidine 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 (for patients with renal impairment see further above).

Patients with other hemorrhagic 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, esophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Other contraindications

Rivaroxaban is contraindicated during pregnancy and breastfeeding. Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban. Rivaroxaban is also contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

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 absorptionin case of overdose may be considered.

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

Individualized bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Hemodynamic support; blood product or component transfusion
- If bleeding cannot be controlled with the above measures, either administration of 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 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 take 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, hemostatic status can also be assessed by Prothrombin time (PT) using Neoplastin as described in the SmPC.

The following coagulation tests are increased: PT, activated partial thromboplastin time (aPTT) and calculated PT international normalized 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 the 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

Indication	Dosing	Special Populations
Stroke prevention in adult patients with non-valvular atrial fibrillation[1]	Rivaroxaban 20 mg once daily	In patient with impaired renal function with CrCL 15-49 ml/min[2] **Rivaroxaban 15 mg once daily** PCI with stent placement for a maximum of 12 months **Rivaroxaban 15 mg once daily** Plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel) PCI with stent placement in patients with impaired renal function with creatinine clearance 30-49 ml/min[2] **Rivaroxaban 10 mg once daily** Plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel)

Treatment of DVT and PE[3], and prevention of recurrent DVT and PE in adult patients	Treatment and prevention of recurrence, day 1-21 **Rivaroxaban 15 mg twice daily** Prevention of recurrence, from day 22 onwards **Rivaroxaban 20 mg once daily** Extended prevention of recurrence, from month 7 onwards **Rivaroxaban 10 mg once daily** Extended prevention of recurrence, from month 7 onwards **Rivaroxaban 20 mg once daily** In patients at high risk of recurrent DVT or PE, such as those: • With complicated comorbidities • Who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10mg.	In patients with impaired renal function with CrCl 15-49ml/min[2] Treatment and prevention of recurrence, day 1-21 **Rivaroxaban 15 mg twice daily** Thereafter **Rivaroxaban 15 mg once daily** instead of rivaroxaban 20 mg once daily if patients assessed risk for bleeding outweighs risk for recurrence When the recommended dose is Rivaroxaban 10 mg once daily, no dose adjustment is necessary
Prevention of VTE in adults Undergoing elective **hip or knee replacement surgery**	**Rivaroxaban 10 mg once daily**	

Rivaroxaban 15 mg and 20 mg must be taken with food

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

1. With one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack.
2. Use with caution in patients with creatinine clearance 15-29 ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.
3. Not recommended as an alternative to unfractionated heparin in patients with PE who are hemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

Reporting of Adverse Drug Reactions

Suspected Adverse Drug Reactions (side effects) and medication errors may bereported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal, and sent by post or email to:

P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Zammit Buildings, Malta Life Sciences Park, San Gwann SGN 3000.

E: postlicensing.medicinesauthority@gov.mt.

Healthcare Professionals may also report any adverse events associated with the use of Rivaroxaban to PharOS Pharmaceutical Oriented Services Single Member Ltd, by phone on +30 210 6664667, online on https://www.pharosgr.gr/contact/, or by email at pharmacovigilance@pharosgr.gr

Please refer to Summary of Product Characteristics (SmPC) before prescribing.
Full prescribing information is available at:
http://www.medicinesauthority.gov.mt/advanced-search

For electronic copies of this Educational Material, please refer to the Malta Medicines Authority website - http://www.medicinesauthority.gov.mt/rmm - **and download the required material with the latest date.**

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