Rivaroxaban Accord 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets

Prescriber Guide

This educational material is provided to further minimise the risk of bleeding that is associated with the use of Rivaroxaban and to guide healthcare professionals in managing that risk.

This Prescriber Guide is not a substitute for the

Rivaroxaban Accord 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets Summary of Product Characteristics (SmPC).
Please consult the SmPC for full prescribing information.

A digital version of the SmPC can be accessed via the EMA website www.ema.europa.eu or Accord website www.accord-healthcare.com.

This is a risk minimisation material and is provided by Accord Healthcare Ltd.

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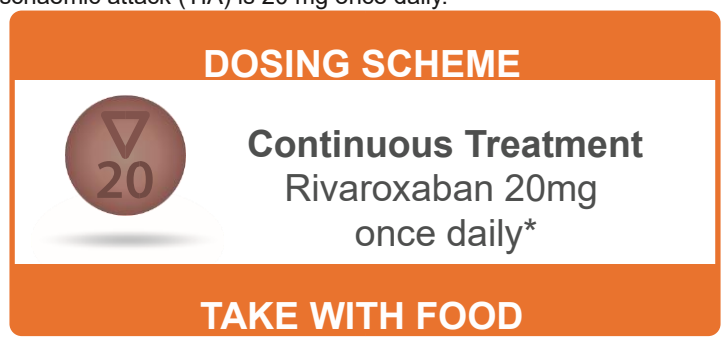
Patient Alert Card

A patient alert card is provided to each patient who is prescribed Rivaroxaban Accord with the product package. The implications of anticoagulant treatment should be explained and the importance of compliance, signs of bleeding and when to seek medical attention discussed with the patient or the caregivers.
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 with them at all times and present it to every healthcare provider, especially if they need to have surgery or other invasive procedures.
Additional copies of the Patient Alert Card can be obtained by contacting local representative: EJ Busuttil Ltd by email: safety@ejbusuttil.com

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 ischaemic attack (TIA) 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

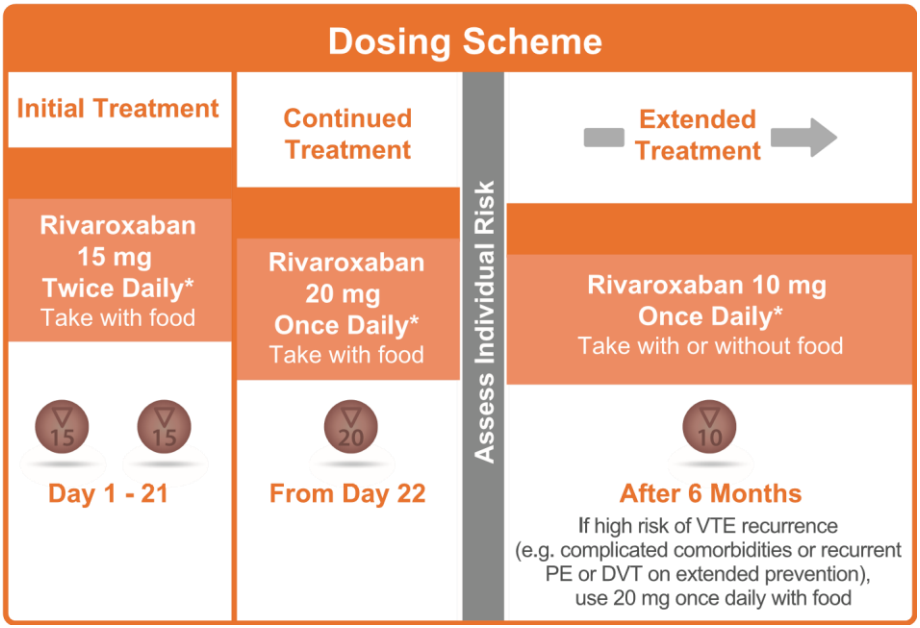
Rivaroxaban can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.

Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients and treatment of VTE and prevention of recurrence in children and adolescents

ADULTS:

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 renal impairment



* 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.

CHILDREN:

For children and adolescents weighing ≥30 kg a Rivaroxaban Accord tablet (15 mg for children 30-<50 kg, 20 mg for children ≥50 kg) once daily can be administered.

The dose is determined based on body weight. The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained.

For patients with body weight less 30 kg refer to the Summary of Product Characteristics of other medicinal products that contain rivaroxaban granules for oral suspension available on the market.

ADULTS:

Patients with moderate (CrCl 30–49 mL/min) or severe (CrCl 15–29 mL/min) renal impairment treated for acute DVT, acute PE and prevention of recurrent DVT and PE should be treated with Rivaroxaban Accord 15 mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is Rivaroxaban Accord 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 risk of bleeding outweighs the risk of recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modelling and has not been studied in this clinical setting. Rivaroxaban Accord 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. When the recommended dose is 10 mg once daily, (after ≥6 months of therapy) no dose adjustment from the recommended dose is necessary.

Rivaroxaban Accord should be used with caution in patients with renal impairment (With moderate renal impairment (CrCl 30-49 mL/min) for Rivaroxaban Accord mg) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

CHILDREN:

No dose adjustment is required for children and adolescents with mild renal impairment (glomerular filtration rate: 50 mL-80 mL/min/1.73 m^2), based on data in adults and limited data in paediatric patients.
Rivaroxaban Accord is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/ min / 1.73 m^2), as no clinical data is available. ***Duration of therapy***

ADULTS:

Short duration of therapy (≥3 months) should be considered in patients with DVT/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/PE not related to major transient risk factors, unprovoked DVT/PE, or a history of recurrent DVT/PE.

CHILDREN:

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data

Patients with renal impairment

available in children to support a dose reduction after 6 months treatment. The benefitrisk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

Missed dose

ADULTS:

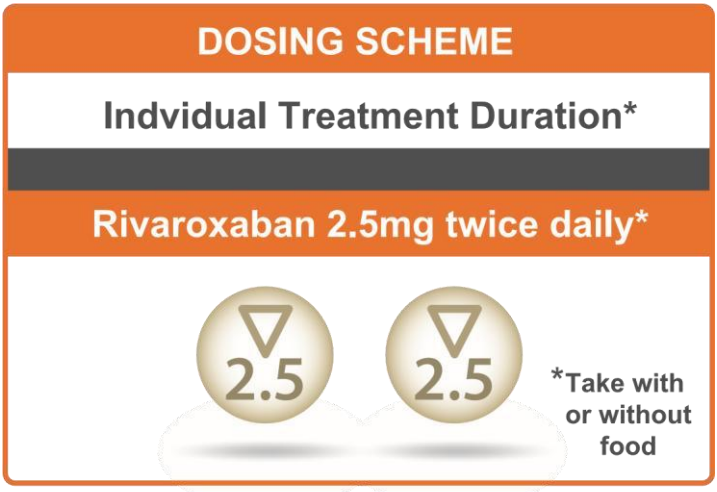
- **Twice daily treatment period** (15 mg bid for the first three weeks): If a dose is missed, the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. Continue with the regular 15 mg twice daily intake on the 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.

CHILDREN:

Once daily regimen

A missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events



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

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

No dose adjustment is required in patients with moderate renal impairment (CrCl 30–49 mL/min). Rixaroxaban 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.

In patients with moderate renal impairment (CrCl 30–49 mL/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, Rixaroxaban 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.

Co-administration with antiplatelet therapy

Patients with renal impairment

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

Other warnings and precautions in CAD/PAD patients

In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Rivaroxaban Accord 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 Rixaroxaban 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided.

Patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months. (see also section 5.1 of the SmPC).

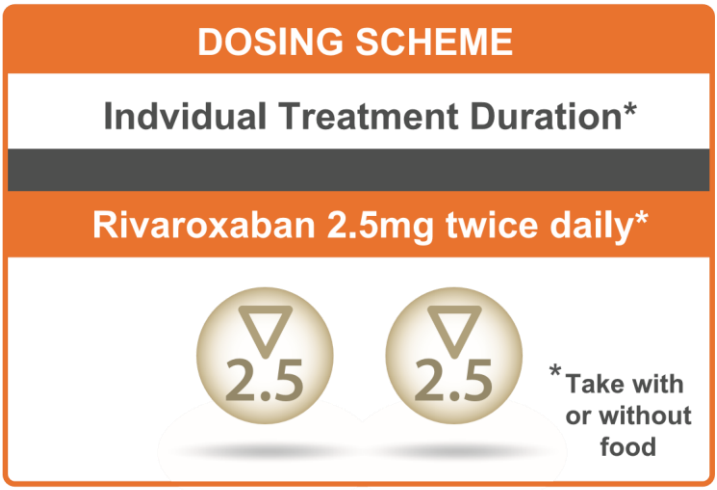
Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.
Concomitant treatment of CAD/PAD with Rixaroxaban 2.5 mg twice daily and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. Treatment with Rixaroxaban 2.5 mg should be avoided in patients with previous stroke or TIA receiving dual antiplatelet therapy.
Rixaroxaban Accord co-administered with ASA should be used with caution in CAD/PAD 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)
- I n CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with Rivaroxaban Accord. (See section 5.1 of the SmPC for further clarification)

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.

Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers



In addition to Rivaroxaban 2.5 mg, patients should also take a daily dose of 75100 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.

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.

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). 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.

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.

Patients with renal impairment

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.

Other warnings and precautions in ACS patients

In recent ACS patients, efficacy and safety of Rivaroxaban Accord 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, 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)

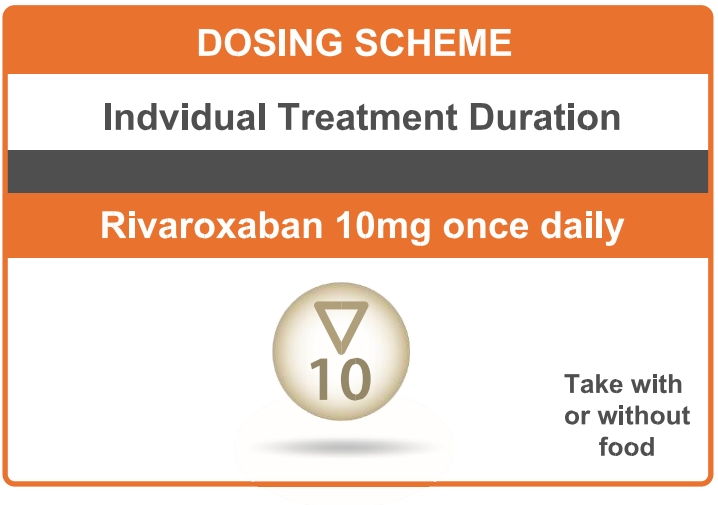
Concomitant treatment of ACS with Rivaroxaban and antiplatelet therapy is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA).

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.

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.



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.

- F or patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended
- F or 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

- R ivaroxaban 2.5 mg and 10mg tablets can be taken with or without food. Rivaroxaban 15 mg and 20 mg are to 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.
- F or 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 tables, the dose should be immediately followed by food.
- T he crushed tablet should be suspended in 50 ml of water and administered 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:

- R ivaroxaban 10/15/20 mg tablets should be stopped at least 24 hours before the intervention.
- R ivaroxaban 2.5 mg tablets should be stopped at least 12 hours before the intervention. 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.

Indication-specific recommendations

- Prevention of stroke and systemic embolism in adult patients with NVAF
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients
- Treatment of VTE and prevention of VTE recurrence in children

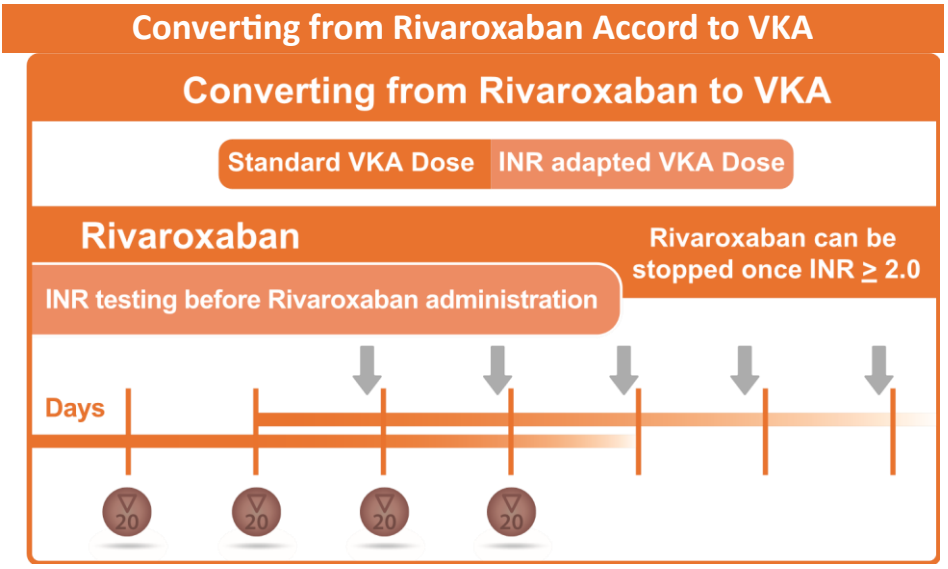
There is no clinical experience with the use of 15 mg and 20 mg Rivaroxaban tablets in adults nor with the use of Rivaroxaban in children in these situations. To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal 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 and should be weighed against the urgency of a 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 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.

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 ≤3.0.

For patients treated for **DVT, PE and prevention of recurrent DVT and PE** and treatment of **VTE and prevention of recurrence in paediatric patients**, 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.



ADULTS:

When converting to VKA, Rivaroxaban and VKA should be given concurrently until the INR ≥2.0. For the first 2 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 **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban.** Once Rivaroxaban has been discontinued, at least 24 hours after last dose, INR values reliably reflect VKA dosing.

CHILDREN:

Children who convert from Rivaroxaban to VKA need to continue Rivaroxaban for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Rivaroxaban. Co-administration of Rivaroxaban and VKA is advised to continue until the INR is ≥ 2.0. 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 Accord

• P atients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban should be started at the time of discontinuation. • P atients 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 Accord to Parental Anticoagulants

Discontinue Rivaroxaban and give the first dose of the parenteral anticoagulant at the time the next Rivaroxaban dose would have been 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
- W ith a lesion or condition, if considered to be a significant risk for 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.
- R eceiving concomitant treatment with any other anticoagulants 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.
- W ith hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.

Adults Only

- C oncomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA)
- C oncomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month

Elderly population: 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.

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

Patients with renal impairment

For adults see dosing recommendations for patients with moderate (CrCl 30–49 mL/ min) or severe (CrCl 15–29 mL/min) renal impairment. Rivaroxaban is to be used with caution in patients with CrCl 15–29 mL/min and in patients with renal impairment (with moderate renal impairment (CrCl 30–49 mL/min) for Rivaroxaban 2.5 mg and 10 mg) concomitantly receiving other medicinal products, that increase rivaroxaban plasma concentrations. Use of Rivaroxaban is not recommended in patients with CrCl <15 mL/ min.

No dose adjustment is required for children and adolescents with mild renal impairment (glomerular filtration rate: 50 mL-80 mL/min/1.73 m^2), based on data in adults and limited data in paediatric patients.
Rivaroxaban Accord is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/ min / 1.73 m^2), as no clinical data is available.

Patients concomitantly receiving other medicinal products

- S ystemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): use of Rivaroxaban is not recommended
- C are is to be taken in patients concomitantly receiving drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- A CS patients and CAD/PAD patients: Patients treated with Rivaroxaban and antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- T he 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)

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The warnings above should be taken into account for the paediatric population.

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
- O ther 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 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 Contraindications

Rivaroxaban is contraindicated during pregnancy and breastfeeding. Women of childbearing 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 in adults; however, no data is available at supratherapeutic doses in children. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found in children, suggesting absorption limitations for higher doses, even when taken together with food. A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa), however, it is not established in children. The use of activated charcoal to reduce absorption in case of overdose may be considered.

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
- 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 (rFVIIa) should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in adults and in children 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.

Dosing Overview in Adults

INDICATION	DOSING	SPECIAL POPULATIONS

Stroke prevention in adult patients with nonvalvular atrial fibrillation[a]	**Rivaroxaban 20 mg once daily**	In patients with impaired renal function with CrCl 15–49 mL/min[b] **Rivaroxaban 15 mg once daily** PCI with stent placement For a maximum of 12 months **Rivaroxaban 15 mg once daily** plus a P2Y12 inhibitor (e.g. clopidogrel) PCI with stent placement in patients with impaired renal function with CrCl 30–49 mL/min[b] **Rivaroxaban 10 mg once daily** plus a P2Y12 inhibitor (e.g. clopidogrel)
Treatment of **DVT** and **PE**[c], 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	In patients with impaired renal function with CrCl 15–49 mL/min[b] Treatment and prevention of recurrence, day 1–21 **Rivaroxaban 15 mg twice daily**

	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 10 mg	Thereafter **Rivaroxaban 15 mg once daily** instead of Rivaroxaban 20 mg once daily if patient's 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	
Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events	**Rivaroxaban 2.5 mg twice daily** **In combination with acetylsalicylic acid** 75-100 mg/day	
Prevention of atherothrombotic events in adult patients after an **ACS** with elevated cardiac biomarkers	**Rivaroxaban 2.5 mg twice daily** **In combination with standard antiplatelet therapy** (acetylsalicylic acid 75-100 mg/day alone or acetylsalicylic acid 75-100 mg/day plus clopidogrel 75 mg/day or a standard dose of ticlodipine)	

Rivaroxaban Accord 15 mg and 20 mg must 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.

[a] With one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

[b] 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.

[c] Not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy

Dosing Overview in Children and Adolescents

For dosing for the treatment of VTE and prevention of recurrence in paediatric patients, please refer to page 4.

Reporting adverse reactions

Reporting suspected adverse events or 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 to Malta Medicine Authority via
the ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.
For further information regarding this medication please contact local representative:
EJ Busuttil Ltd.
Phone: 21447184 (service is available 24/7)
Email: safety@ejbusuttil.com Office Adress:
Busuttil Buildings, Triq l-Għadam,
Central Business District Zone 1,
Birkirkara CBD1060 MALTA
Adverse reactions should also be reported to Accord Healthcare by calling 0044 1271 385 257 or by emailing: medinfo@accord-healthcare.com.
The educational material has been prepared with the aim of ensuring safe and efficient use of themedication and adequate risk management and it has been approved by Malta Medicines Authority on 05/03/2026.