Rivaroxaban Torrent Prescriber Guide

Version number 1.0
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This guide is to be used to support the appropriate use of Rivaroxaban in the following indications:

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

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, which is available on Torrent Pharma UK Ltd website:
https://torrentpharmauk.healthcare/rivaroxaban

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

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

Please instruct patients 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.

Contents

ADULT: STROKE PREVENTION IN NON-VALVULAR AF

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.

DOSING RECOMMENDATIONS

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

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

Patients with renal impairment:

In patients with moderate (creatinine clearance 30-49ml/min) or severe (15-29ml/min) renal impairment the recommended dose is 15mg 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 < 15ml/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 15mg Rivaroxaban once daily (or 10mg Rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30-49ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial

fibrillation who require oral anticoagulation and undergo PCI with stent placement.

Patients undergoing cardioversion:

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

ORAL INTAKE

Rivaroxaban 15mg and 20mg 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 15mg or 20mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

PERIOPERATIVE MANAGEMENT

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

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

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

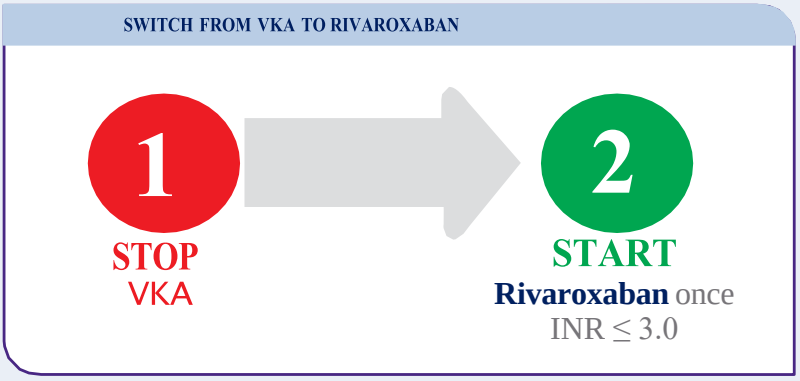
Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15mg or 20mg Rivaroxaban in these situations.

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

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

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

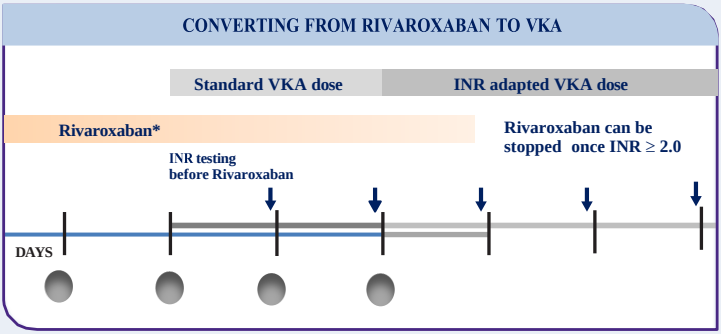
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



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

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

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose

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

When converting to VKA, Rivaroxaban and VKA should 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 be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

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

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN

The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS

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

- With clinically significant active bleeding
- With a lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal

ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

- Receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), LMWH (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy to or from Rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

- With hepatic disease associated with coagulopathy and clinically relevant bleeding risk including Child-Pugh class B and C cirrhotic patients.

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients

- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban.

- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy.

SPECIAL POPULATIONS

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 done after assessment of treatment benefit against the risk of bleeding:

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

- ***Patients concomitantly receiving other medicinal products:***
  - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
  - Care is to be taken in patients concomitantly receiving drugs

affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

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

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

- ***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.

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.

HOW TO MANAGE BLEEDING COMPLICATIONS

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

Individualised bleeding management may include:

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

COAGULATION TESTING

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

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

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

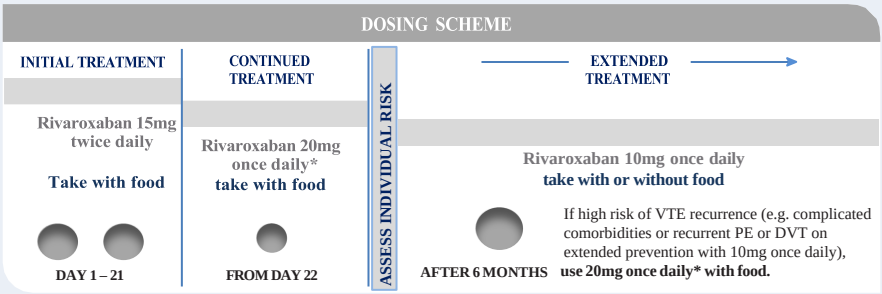
ADULT AND CHILDREN: TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE

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

DOSING RECOMMENDATIONS

Adults

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



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

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10mg **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 10mg **once daily**, a dose of Rivaroxaban 20mg **once daily** should be considered.

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

Children

Rivaroxaban is not recommended for use in children less than 6 months of age who:

- at birth had <37 weeks gestation, or
- have a body weight of less than 2.6kg, or
- who have had less than 10 days of oral feeding.

The dose of Rivaroxaban cannot be reliably determined in these children and has not been studied.

For all other children, Rivaroxaban treatment should be initiated following ≥5 days of initial anticoagulation treatment with parenteral heparins.

Dosing is based on body weight. To ensure that a therapeutic dose is maintained, the weight of the child should be monitored and the dose reviewed regularly, especially for children below 12kg. Dose adjustments should be made based on changes in body weight only.

Rivaroxaban 15mg Tablets, Rivaroxaban 20mg Tablets or Rivaroxaban 1mg/ml granules* for oral suspension can be used to achieve the appropriate weight-based dose.

- For children weighing >2.6kg and <30kg, use the granules for oral suspension*.
- For children and adolescents weighing ≥30 and <50kg, use the 15mg tablet or granules for oral suspension**.
- For children and adolescents weighing ≥50kg, use the 20mg tablet or granules for oral suspension*.

* The granules for oral suspension are not currently licensed and marketed by Torrent Pharma (UK) Ltd.

**15mg and 20mg tablets are only indicted for a paediatric population weighing from 30 kg to 50 kg (15mg) or weighing more than 50 kg (20mg)

Recommended dose for Rivaroxaban in paediatric patients from full-term neonates (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children less than 18 years of age

Pharmaceutical form	**Body weight [kg]**		**Regimen (1mg Rivaroxaban= 1ml suspension)**			**Total daily dose (1mg=1ml suspension)**	**Suitable blue syringe**
	Min	**Max**	**OD once a day**	**BID 2 times a day**	**TID 3 times a day**		
Oral suspension	2.6	< 3			0.8mg	2.4mg	1ml
	3	< 4			0.9mg	2.7mg	1ml
	4	< 5			1.4mg	4.2mg	5ml
	5	< 7			1.6mg	4.8mg	5ml
	7	< 8			1.8mg	5.4mg	5ml
	8	< 9			2.4mg	7.2mg	5ml
	9	< 10			2.8mg	8.4mg	5ml
	10	< 12			3.0mg	9.0mg	5ml
	12	< 30		5mg		10mg	5ml or 10ml
Tablets or oral suspension	30	< 50	15mg			15mg	10ml
	≥ 50		20mg			20mg	10ml

Patients with renal impairment:

Adults

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

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

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

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

Children

No dose adjustment is required for children aged ≥1 year with mild renal impairment (glomerular filtration rate: 50ml ≤ 80ml/min/1.73m^2), based on data in adults and limited data in paediatric patients.

Rivaroxaban is not recommended in children aged ≥1 year with moderate or severe renal impairment (glomerular filtration rate <50ml/min/1.73m^2), as no clinical data is available.

In children aged <1 year, estimation of serum creatinine instead of GFR is applied. Rivaroxaban is not recommended in children aged <1 year with serum creatinine results above 97.5th percentile, as no clinical data is available.

*with moderate renal impairment (CrCL 30-49ml/min) for Rivaroxaban 10mg

Duration of therapy:

Adults

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

Children

All children, except those aged <2 years with catheter-related thrombosis

Therapy with Rivaroxaban should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. The benefit-risk 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.

Children aged <2 years with catheter-related thrombosis

Therapy with Rivaroxaban should be continued for at least 1 month. Treatment can be extended up to 3 months when clinically necessary. The benefit-risk of continued therapy after 1 month 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** (15mg bid for the first three weeks): If a dose is missed, the patient should take Rivaroxaban immediately to ensure intake of 30mg Rivaroxaban per day. In this case two 15mg tablets may be taken at once. Continue with the regular 15mg 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

- **Two times daily regimen:** A missed morning dose should be taken

immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken in the same evening

- **Three times daily regimen:** The three times daily administration schedule with approximately 8-hour intervals should be resumed at the next scheduled dose without compensating for the missed dose

On the following day, the child should continue with the regular once, twice, or three times daily regimen.

ORAL INTAKE

Rivaroxaban 15mg and 20mg tablets and 1mg/ml granules for oral suspension 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.

Adults

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 15mg or 20mg film- coated tablets, the dose should then be immediately followed by enteral feeding.

Children

For children weighing ≥ 30kg who are unable to swallow whole tablets, Rivaroxaban granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of Rivaroxaban 15mg of 20mg are prescribed, these could be provided by crushing the 15mg or 20mg tablet and mixing it with water or soft foods such as apple puree immediately prior to use and administered orally.

The oral suspension and the crushed Rivaroxaban tablet may be given through nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Rivaroxaban. Avoid administration of

Rivaroxaban distal to the stomach.

PERIOPERATIVE MANAGMENT

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

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

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

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

Patients must be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of Rivaroxaban 15mg or 20mg tablets in adults nor with the use of Rivaroxaban in children in these situations.

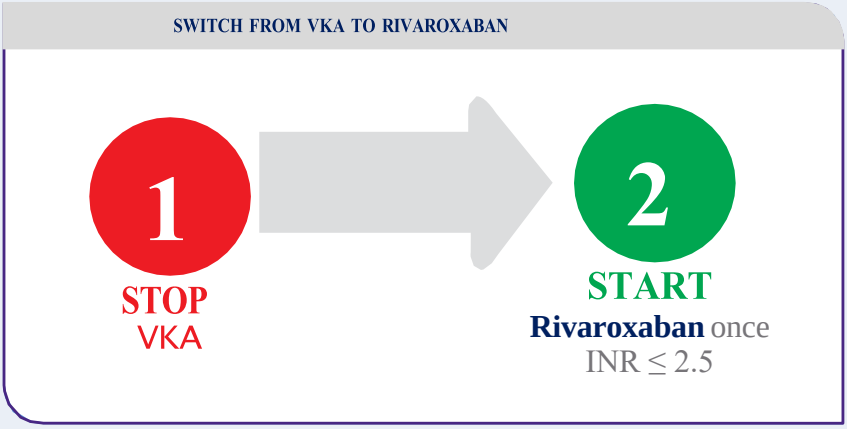
To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant 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 placement/removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least

18 hours in young 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.

No data is available on the placement or removal of a neuraxial catheter in children while on Rivaroxaban. Discontinue Rivaroxaban and consider a short acting parenteral anticoagulant.

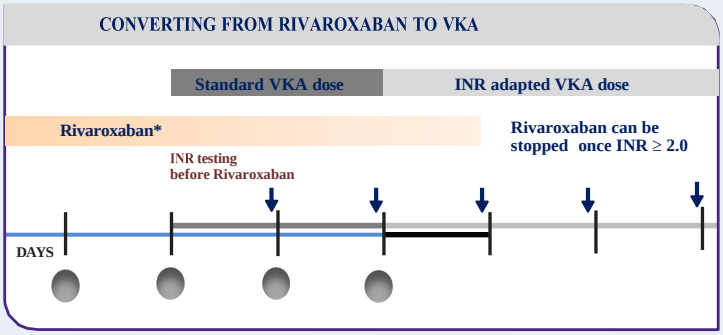
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



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

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

Converting From Rivaroxaban to VKA



* See dosing recommendations for required daily dose

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

Adults and children

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 be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

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.

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 adults and children:

- 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:
  - In children, Rivaroxaban is contraindicated based on the data obtained in adults as no clinical data is available in children with hepatic impairment

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. Treatment decision in these patients should be done after assessment of treatment benefit against the risk of bleeding:

- ***Patients with renal impairment:***

  - For adults, see "dosing recommendations" section for patients with renal impairment
  - In children aged ≥1 year no dose adjustment is required with mild renal impairment (glomerular filtration rate: 50-80ml/min/1.73m^2). Rivaroxaban is not recommended in children aged ≥1 year with moderate or severe renal impairment (glomerular filtration rate <50 ml/min/1.73m^2), as no clinical data is available.

  Rivaroxaban is not recommended in children aged <1 year with serum creatinine results above 97.5th percentile, as no clinical data is available.

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

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

- ***Patients with other haemorrhagic risk factors:***

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

  In adults:

  - 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

In children:

- congenital or acquired bleeding disorders
- uncontrolled 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

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 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, suggesting absorption limitations for higher doses, even when taken together with food in children. A specific reversal agent antagonising the pharmacodynamic effect of Rivaroxaban is available (refer to the SmPC 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.

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

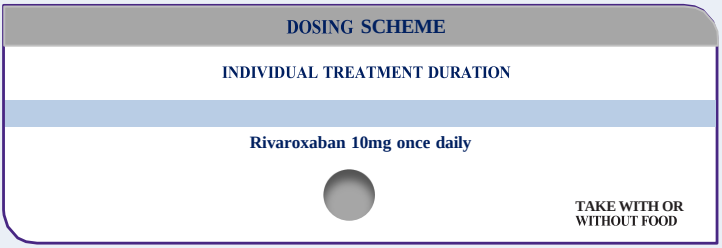
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR).

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

DOSING RECOMMENDATIONS

The recommended dose is 10mg Rivaroxaban taken orally **once daily**. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.



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

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

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:

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

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

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

Missed dose:

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

ORAL INTAKE

Rivaroxaban 10mg can be taken with or without food.

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

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

PERIOPERATIVE MANAGEMENT

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

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk 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 are to be frequently monitored for signs and symptoms of neurological

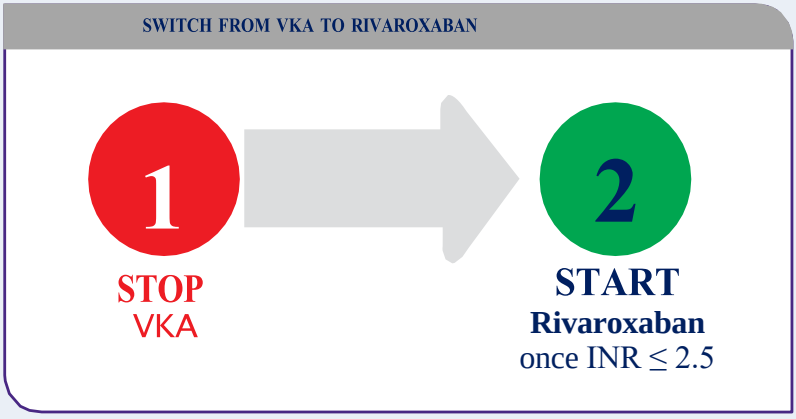
impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

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

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

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

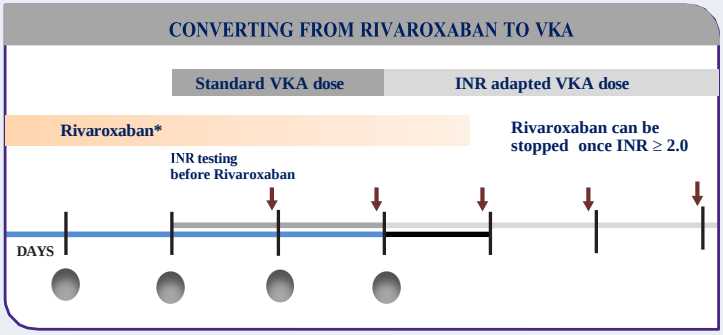
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN



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

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

CONVERTING FROM RIVAROXABAN TO VKA



* See dosing recommendations for required daily dose

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

When converting to VKA, Rivaroxaban and VKA should 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 be tested the next day, just before the next dose of Rivaroxaban (but not within 24 hours of the previous dose; any sooner and Rivaroxaban will interfere with the INR result).** Once Rivaroxaban has been discontinued, after 24 hours, INR values reliably reflect VKA dosing.

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

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

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS

The first dose of the parenteral anticoagulant should be given at the time the next Rivaroxaban dose would have been taken.

CONTRAINDICATIONS

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

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

Rivaroxaban is also contraindicated in the following situations:

- Hypersensitivity to the active substance or to any of the excipients
- During pregnancy. Women of child-bearing potential should avoid becoming pregnant during treatment with Rivaroxaban.

- During breastfeeding. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy

SPECIAL POPULATIONS

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

- ***Patients with renal impairment:*** See "dosing recommendations" section for patients with renal impairment.
- ***Patients concomitantly receiving other medicinal products:***
  - Use of Rivaroxaban is not recommended with systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)
  - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- ***Patients with other haemorrhagic risk factors:***

  As with other antithrombotic, 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.

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.

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 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-(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]	SPECIAL PATIENT POPULATIONS[1]
Stroke prevention in adult patients with non-valvular atrial fibrillation[a]	**Rivaroxaban 20mg once daily** Impaired renal function with CrCl 15-49ml/min[b]: **Rivaroxaban 15mg once daily**	**PCI with stent placement** (for max. 12 months): - **Rivaroxaban 15mg once daily** plus a P2Y12 inhibitor (e.g. clopidogrel) - **Rivaroxaban 10mg once daily** plus a P2Y12 inhibitor (e.g. clopidogrel) for patients with impaired renal function (CrCl 30-49ml/min[b])
Treatment of **DVT** and **PE**[c], and prevention of recurrent DVT and PE:		
Adults	**Treatment & prevention of recurrence:** Day 1-21: **Rivaroxaban 15mg twice daily** **Prevention of recurrence:** Day 22 onwards: **Rivaroxaban 20mg once daily** *Impaired renal function with CrCl 15-49ml/min*[b]: **Rivaroxaban 15mg once daily**, if patient's assessed risk for bleeding outweighs risk for recurrence **Extended prevention of recurrence:** After at least 6 months treatment: **Rivaroxaban 10mg once daily**	**Extended prevention of recurrence in high-risk patients: Rivaroxaban 20mg once daily** for extended prevention of recurrence, after at least 6 months treatment, 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

Children – dosing is based on body weight	**Rivaroxaban is not recommended for use in children less than 6 months of age who:** - at birth had <37 weeks gestation, or - have a body weight of less than 2.6kg, or - who have had less than 10 days of oral feeding. The dose of Rivaroxaban cannot be reliably determined in these children and has not been studied. For all other children, Rivaroxaban treatment should be initiated following ≥5 days of initial anticoagulation treatment with parenteral heparins. Dosing is based on body weight. To ensure that a therapeutic dose is maintained, the weight of the child should be monitored, and the dose reviewed regularly, especially for children below 12kg. Dose adjustments should be made based on changes in body weight only. Rivaroxaban 15mg Tablets, Rivaroxaban 20mg Tablets or Rivaroxaban 1mg/mL granules for oral suspension[d] can be used to achieve the appropriate weight-based dose. For children weighing >2.6kg and <30kg, use the granules for oral suspension. For children and adolescents weighing ≥30 and <50kg, use the 15mg tablet or granules for oral suspension[d]. For children and adolescents weighing ≥50kg, use the 20mg tablet or granules for oral suspension[d].	

Prevention of VTE in adults undergoing elective **hip or knee replacement surgery**	**Rivaroxaban 10mg once daily** **Hip Replacement Surgery** 5 weeks treatment duration **Knee Replacement Surgery** 2 weeks treatment duration	
Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events	**Rivaroxaban 2.5mg[e] 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[e] 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)	

Rivaroxaban 15mg and 20mg should 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.

[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 15-29ml/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 hemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.
[d] Granules for oral suspension are not currently licensed and marketed by Torrent Pharma (UK) Ltd
[e] Rivaroxaban 2.5 mg film-coated tablets are not currently marketed by Torrent Pharma (UK)Ltd

Reference: 1. Rivaroxaban (rivaroxaban). Summary of Product Characteristics.

NOTES

Reporting adverse events and quality complaints

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard . Adverse events should also be reported to Torrent Pharma UK Ltd.

To report any Adverse Events to Torrent Pharma (UK) Ltd or obtain Medical Information on Torrent UK products: Telephone: 0800 088 5366 · Email: Medinfo.Torrent@apcerls.com