

PRESCRIBER GUIDE

for

**Rivaroxaban Abdi 2.5 mg, 10 mg, 15 mg and 20 mg
Film-coated tablets**

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

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke
- Treatment of deep vein 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 Abdi in order to minimise the risk of bleeding during treatment with Rivaroxaban Abdi.

The Prescriber Guide does not substitute the Rivaroxaban Abdi Summary of Product Characteristics (SmPC)

Rivaroxaban Abdi patient alert card

A patient alert card is provided with the product package to each patient who is prescribed Rivaroxaban Abdi.

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 15 mg and 20 mg only)
- Recognising signs or symptoms of bleeding
- When to seek medical attention

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

Please instruct patients 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 | 4 |
| ADULT AND CHILDREN: TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE | 11 |
| ADULT: PREVENTION OF VTE IN ADULT PATIENTS UNDERGOING ELECTIVE HIP OR KNEE REPLACEMENT SURGERY | 20 |
| ADULT: USE IN CORONARY ARTERY DISEASE (CAD) AND PERIPHERAL ARTERY DISEASE (PAD)..... | 26 |
| ADULT: USE IN ACS _{sp} (ACUTE CORONARY SYNDROME SECONDARY PREVENTION)..... | 33 |

ADULT: STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION (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 20 mg once daily.

| Dosing Scheme |
|---|
| Continuous Treatment |
| Rivaroxaban Abdi 20 mg once daily* |
|  TAKE WITH FOOD |

* 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 15 mg once daily. Rivaroxaban Abdi 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 Abdi should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase Rivaroxaban Abdi plasma concentrations.

Duration of therapy:

Rivaroxaban Abdi 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 Abdi 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 Abdi once daily (or 10mg Rivaroxaban Abdi 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 Abdi 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 Abdi treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.

ORAL INTAKE

Rivaroxaban Abdi 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 Abdi 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 Abdi 15mg or 20mg film-coated tablets, the dose should be immediately followed by food.

The crushed Rivaroxaban Abdi 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 Abdi 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 Abdi 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 Abdi should be assessed against the urgency of the intervention.

Rivaroxaban Abdi 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 15 mg or 20 mg Rivaroxaban Abdi in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban Abdi and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Abdi. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Abdi 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 Abdi (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban Abdi dose is administered.

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

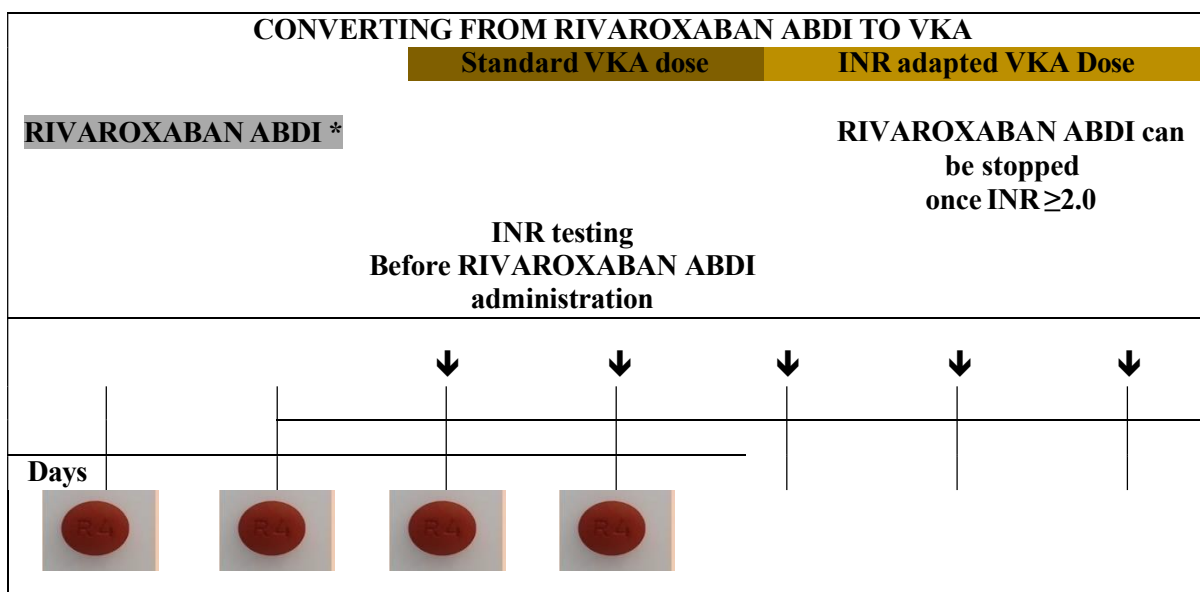
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN ABDI



For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and Rivaroxaban Abdi 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 ABDI 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 Abdi 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 ABDI:

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban Abdi 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 Abdi 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN ABDI TO PARENTERAL ANTICOAGULANTS:

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

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban Abdi may increase the risk of bleeding. Therefore, Rivaroxaban Abdi 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 Abdi 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 Abdi 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 Abdi
- 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 Abdi 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 Abdi 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 Abdi have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Abdi provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Abdi 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 Abdi therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban Abdi 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 Abdi 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 Abdi, the next Rivaroxaban Abdi 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 Abdi. Due to the high plasma protein binding Rivaroxaban Abdi is not expected to be dialysable.

COAGULATION TESTING

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

Anti-FXa assays with Rivaroxaban Abdi -(Rivaroxaban) specific calibrators to measure Rivaroxaban Abdi 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 Abdi. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban Abdi 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.

| DOSING SCHEME | | | |
|--|---|------------------------|---|
| Initial treatment | Continued treatment | Extended treatment | |
| Rivaroxaban Abdi 15mg twice daily TAKE WITH FOOD | Rivaroxaban Abdi 20mg once daily* TAKE WITH FOOD | Assess individual risk | Rivaroxaban Abdi 10mg once daily TAKE WITH OR WITHOUT FOOD If high risk of VTE recurrence (e.g., complicated comorbidities or recurrent PE or DVT on extended prevention with 10mg once daily), use 20mg once daily* with food. |
| DAY 1-21  | FROM DAY 22  | | AFTER 6 MONTHS  |

* 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 Abdi 10mg **once daily**, a dose of Rivaroxaban Abdi 20mg once daily should be considered.

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

Children

For children and adolescent <18 years, Rivaroxaban Abdi treatment should be initiated following ≥ 5 days of initial anticoagulation treatment with parenteral heparins.

The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Rivaroxaban products formulated as granules for oral suspension.

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. Dose adjustments should be made based on changes in body weight only.

Patients with renal impairment:

Adults

Rivaroxaban Abdi 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 15-29 ml/min) indicate that Rivaroxaban Abdi plasma concentrations are significantly increased. Therefore, Rivaroxaban Abdi 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 Abdi should be used with caution in patients with renal impairment* concomitantly receiving other medicinal products which increase Rivaroxaban Abdi plasma concentrations.

Children

No dose adjustment is required for children and adolescents with mild renal impairment (glomerular filtration rate: $50\text{ml} \leq 80\text{ml}/\text{min}/1.73\text{m}^2$), based on data in adults and limited data in paediatric patients.

Rivaroxaban Abdi is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate $<50\text{ml}/\text{min}/1.73\text{m}^2$), as no clinical data is available.

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

Therapy with Rivaroxaban Abdi should be continued for at least 3 months in children and adolescents. 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.

Missed dose:

Adults

- **Twice daily treatment period** (15mg bid for the first three weeks): If a dose is missed, the patient should take Rivaroxaban Abdi immediately to ensure intake of 30mg Rivaroxaban Abdi 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 Abdi 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 Abdi 15mg and 20mg tablets 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 Abdi 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 Abdi 15mg or 20mg film-coated tablets, the dose should be immediately followed by food.

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

Children

For children weighing ≥ 30 kg who are unable to swallow whole tablets, Rivaroxaban Abdi granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of Rivaroxaban Abdi 15mg or 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 Abdi tablet may be given through nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Rivaroxaban Abdi. Avoid administration of Rivaroxaban Abdi distal to the stomach.

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, Rivaroxaban Abdi 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 Abdi should be assessed against the urgency of the intervention.

Rivaroxaban Abdi 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 Abdi 15mg or 20mg tablets in adults nor with the use of Rivaroxaban Abdi in children in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban Abdi and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Abdi. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Abdi 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 Abdi (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban Abdi dose is administered.

If traumatic puncture occurs the administration of Rivaroxaban Abdi 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 Abdi. Discontinue Rivaroxaban Abdi and consider a short acting parenteral anticoagulant.

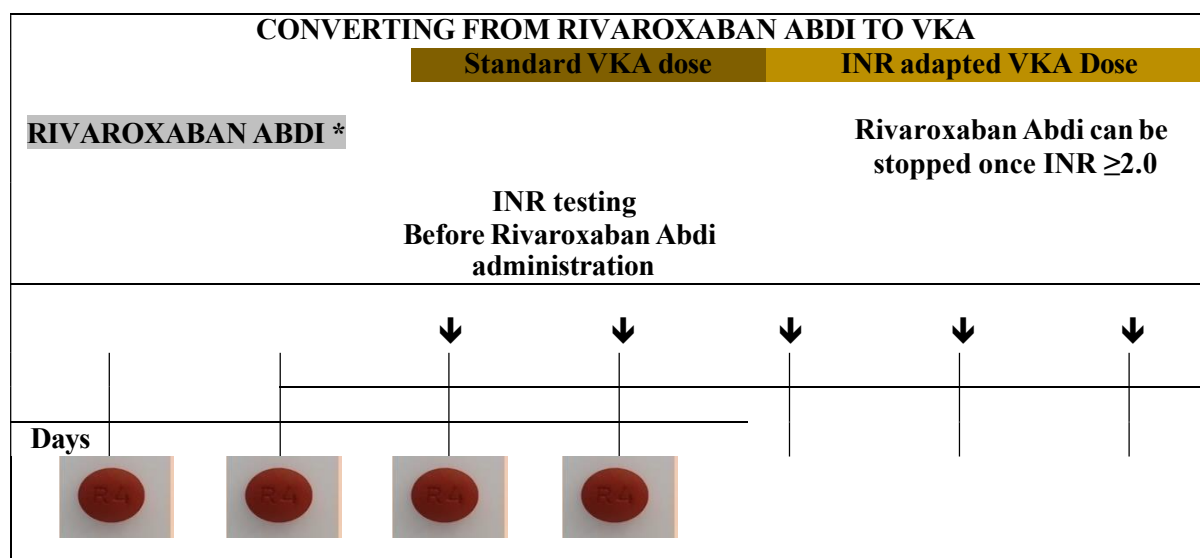
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN ABDI



For patients treated for DVT, PE and prevention of recurrent DVT and PE, treatment with VKA should be stopped and Rivaroxaban Abdi 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 ABDI TO VKA



* See dosing recommendation 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 Abdi 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 Abdi to VKA need to continue Rivaroxaban Abdi 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 Abdi. Co-administration of Rivaroxaban Abdi and VKA is advised to continue until the INR is ≥ 2.0 .

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN ABDI

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban Abdi 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 Abdi 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN ABDI TO PARENTERAL ANTICOAGULANTS

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

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban Abdi may increase the risk of bleeding. Therefore, Rivaroxaban Abdi 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 Abdi 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 Band C cirrhotic patients”
 - In children, Rivaroxaban Abdi is contraindicated based on the data obtained in adults as no clinical data is available in children with hepatic impairment.

Rivaroxaban Abdi 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 Abdi.
- 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 and adolescents, no dose adjustment is required with mild renal impairment (glomerular filtration rate: 50-80ml/min/1.73m²). Rivaroxaban Abdi is not recommended in children and adolescents, with moderate or severe renal impairment (glomerular filtration rate < 50 ml/min/1.73m²), as no clinical data is available.

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

- Use of Rivaroxaban Abdi 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 antithrombotics, Rivaroxaban Abdi 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 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 Abdi have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Abdi provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Abdi 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 Abdi therapy.

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

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 Abdi 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 Abdi is available, 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 Abdi, the next Rivaroxaban Abdi 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 receiving Rivaroxaban Abdi. Due to the high plasma protein binding Rivaroxaban is not expected to be dialysable.

COAGULATION TESTING

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


Anti-FXa assays with Rivaroxaban Abdi -(Rivaroxaban) specific calibrators to measure Rivaroxaban Abdi 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 Abdi. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban Abdi 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 Abdi taken orally **once daily**. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

| DOSING SCHEME | |
|---|----------------------------------|
| Individual Treatment Schedule | |
| Rivaroxaban Abdi 10mg once daily | |
|  | TAKE WITH OR WITHOUT FOOD |

Patients with renal impairment:

Rivaroxaban Abdi 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 < 15 ml/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 Abdi plasma concentrations Rivaroxaban Abdi 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 Abdi 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 Abdi 10mg can be taken with or without food.

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

The crushed Rivaroxaban Abdi 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 Abdi 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 Abdi 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 Abdi and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Abdi. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Abdi 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 Abdi 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 Abdi dose is administered.

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

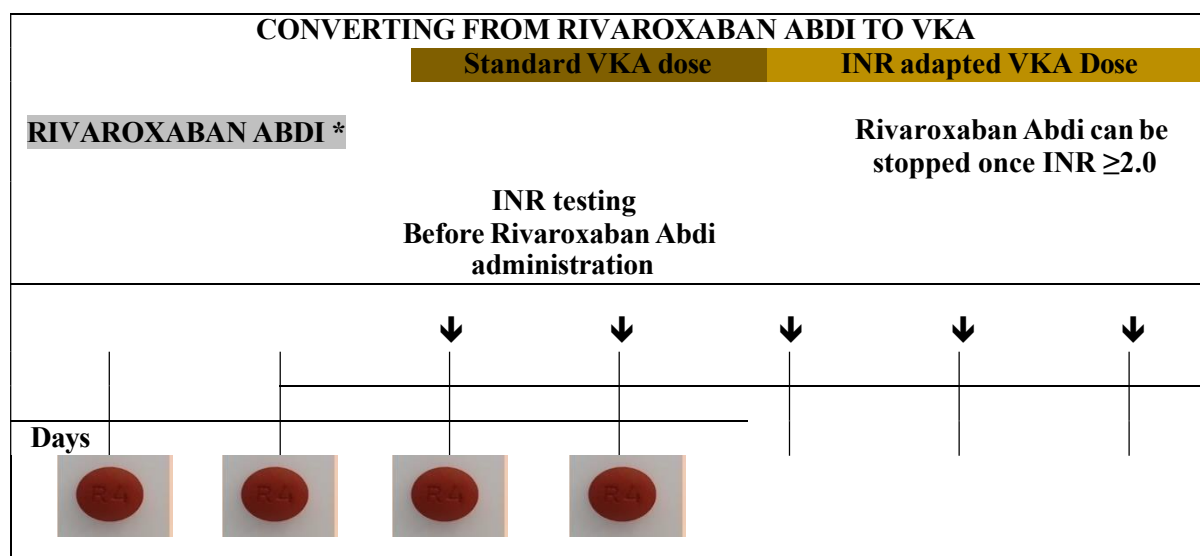
CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN ABDI



For patients treated for **DVT, PE and prevention of recurrent DVT and PE**, treatment with VKA should be stopped and Rivaroxaban Abdi 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 ABDI 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 Abdi and VKA should overlap until the **INR is ≥ 2.0** . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

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

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN ABDI

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban Abdi 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 Abdi 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN ABDI TO PARENTERAL ANTICOAGULANTS

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

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban Abdi may increase the risk of bleeding. Therefore, Rivaroxaban Abdi 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 Abdi 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 Band C cirrhotic patients.

Rivaroxaban Abdi 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 Abdi.
- 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 Abdi 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 Abdi 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 Abdi 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 Abdi have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Abdi provides adequate

anticoagulation in this patient population. Treatment with Rivaroxaban Abdi 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 Abdi therapy. In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban Abdi 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 Abdi 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 Abdi, the next Rivaroxaban Abdi 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 receiving Rivaroxaban Abdi. Due to the high plasma protein binding Rivaroxaban Abdi is not expected to be dialysable.

COAGULATION TESTING

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

Anti-FXa assays with Rivaroxaban Abdi -(Rivaroxaban) specific calibrators to measure Rivaroxaban Abdi 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 Abdi. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban Abdi to VKA as described above.

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

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

DOSING RECOMMENDATIONS

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

| DOSING SCHEME |
|--|
| INDIVIDUAL TREATMENT DURATION* |
| Rivaroxaban Abdi 2.5 mg twice daily* |
|  TAKE WITH OR WITHOUT FOOD |

* See dosing recommendations for required daily dose

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

Patients with renal impairment:

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

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

Duration of therapy:

Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

Missed dose:

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

ORAL INTAKE

Rivaroxaban Abdi 2.5mg can be taken with or without food. For patients who are unable to swallow whole tablets, a Rivaroxaban Abdi tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed Rivaroxaban Abdi 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 Abdi 2.5mg should be stopped at least 12 hours before the intervention if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban Abdi should be assessed against the urgency of the intervention. Rivaroxaban Abdi 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.

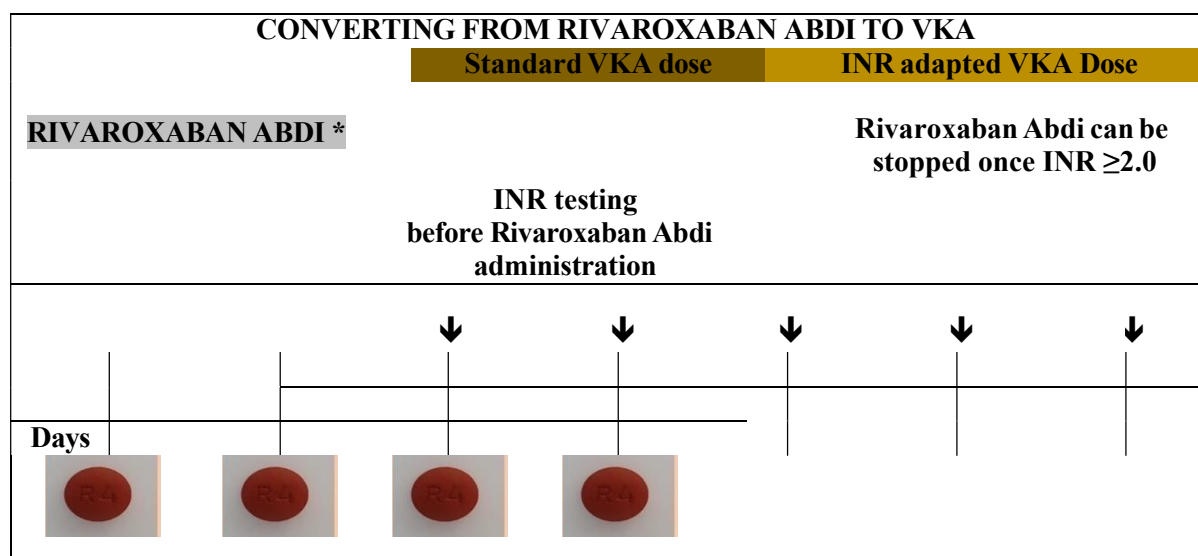
There is no clinical experience with the use of Rivaroxaban Abdi 2.5mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information. To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban Abdi and neuraxial (epidural/ spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Abdi. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Abdi is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN ABDI



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 ABDI 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 Abdi 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 ABDI

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban Abdi 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 Abdi 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN ABDI TO PARENTERAL ANTICOAGULANTS

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

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban Abdi may increase the risk of bleeding. Therefore, Rivaroxaban Abdi 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 Abdi 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 Band C cirrhotic patients.
- With ACS who had a prior stroke or a transient ischaemic attack (TIA) and are receiving antiplatelet therapy.

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

Rivaroxaban Abdi 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 Abdi.
- 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 Abdi 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.

- **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 Abdi 2.5mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.

- **Patients with renal impairment:** See "dosing recommendations" section for patients with renal impairment.
- **Patients concomitantly receiving other medicinal products:**
 - Use of Rivaroxaban Abdi 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 being treated for CAD or PAD with Rivaroxaban Abdi and antiplatelet agents only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk.
- **Patients with other haemorrhagic risk factors:**
As with other antithrombotics, Rivaroxaban Abdi 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 Abdi have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Abdi provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Abdi 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 Abdi therapy. In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban Abdi is contraindicated.
- **Rivaroxaban Abdi should be used with caution in CAD/PAD patients:**
Rivaroxaban Abdi 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)
 - In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with Rivaroxaban Abdi. (See section 5.1 of the SmPC for further clarification)
- **Other warnings and precautions in CAD/PAD patients**
In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Rivaroxaban Abdi 2.5 mg twice daily have been investigated in combination with ASA. In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Rivaroxaban Abdi 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

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Rivaroxaban Abdi 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 Abdi, the next Rivaroxaban Abdi 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 receiving Rivaroxaban Abdi. Due to the high plasma protein binding RIVAROXABAN ABDI is not expected to be dialysable.

COAGULATION TESTING

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

Anti-FXa assays with Rivaroxaban Abdi -(Rivaroxaban) specific calibrators to measure Rivaroxaban Abdi 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 (aPTI) 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 Abdi. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban Abdi to VKA as described above.

**ADULT: USE IN ACS_{sp} (ACUTE CORONARY SYNDROME
SECONDARY PREVENTION)**

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

DOSING RECOMMENDATIONS

| DOSING SCHEME | |
|---|----------------------------------|
| Individual Treatment Duration* | |
| Rivaroxaban Abdi 2.5 mg twice daily* | |
|  | TAKE WITH OR WITHOUT FOOD |

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

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

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

Patients with renal impairment:

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

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

Duration of therapy:

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

Missed dose:

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

ORAL INTAKE

Rivaroxaban Abdi 2.5mg can be taken with or without food. For patients who are unable to swallow whole tablets, a Rivaroxaban Abdi tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally.

The crushed Rivaroxaban Abdi 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 Abdi 2.5mg should be stopped at least 12 hours before the intervention if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding due to Rivaroxaban Abdi should be assessed against the urgency of the intervention.

Rivaroxaban Abdi 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.

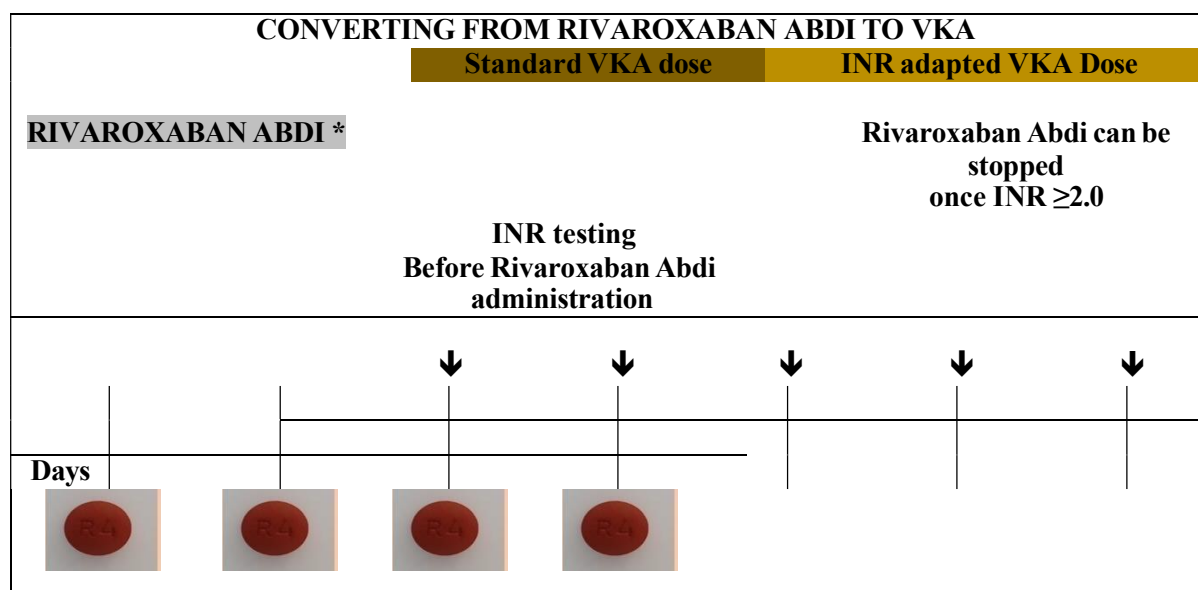
There is no clinical experience with the use of Rivaroxaban Abdi 2.5mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information. To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban Abdi and neuraxial (epidural/ spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Abdi. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Abdi is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN ABDI



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

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

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN ABDI

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Rivaroxaban Abdi 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 Abdi 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

CONVERTING FROM RIVAROXABAN ABDI TO PARENTERAL ANTICOAGULANTS

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

CONTRAINDICATIONS

Like all anticoagulants, Rivaroxaban Abdi may increase the risk of bleeding. Therefore, Rivaroxaban Abdi 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 Abdi 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 Band C cirrhotic patients.
- With ACS who had a prior stroke or a transient ischaemic attack (TIA) and are receiving antiplatelet therapy.

Rivaroxaban Abdi 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 Abdi .
- 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 Abdi 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.

- **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 Abdi 2.5mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.
- **Patients with renal impairment:** See "dosing recommendations" section for patients with renal impairment.
- **Patients concomitantly receiving other medicinal products:**
 - Use of Rivaroxaban Abdi 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).
 - After an acute coronary syndrome patients treated with Rivaroxaban Abdi and antiplatelet agents only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
 - The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (For patients with renal impairment see further above).
- **Patients with other haemorrhagic risk factors:**
As with other antithrombotics, Rivaroxaban Abdi 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 Abdi have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Abdi provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Abdi 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 Abdi therapy. In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban Abdi is contraindicated.
- **Other warnings and precautions in ACS patients**
In recent ACS patients, efficacy and safety of Rivaroxaban Abdi 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 Abdi should be used with caution in ACS patients**
In recent ACS patients, efficacy and safety of Rivaroxaban Abdi 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 Abdi, 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 Abdi and antiplatelet therapy is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA).

OVERDOSE

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg Rivaroxaban Abdi 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 Abdi, the next Rivaroxaban Abdi 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 receiving Rivaroxaban Abdi. Due to the high plasma protein binding Rivaroxaban Abdi is not expected to be dialysable.

COAGULATION TESTING

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

Anti-FXa assays with Rivaroxaban Abdi -(Rivaroxaban) specific calibrators to measure Rivaroxaban Abdi 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 (aPTI) 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 Abdi. Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban Abdi to VKA as described above.

DOSING OVERVIEW TABLE

Please consult SmPC for full product information.

| INDICATION ¹ | DOSING ¹ | SPECIAL PATIENT POPULATIONS ¹ |
|---|---|--|
| <p>Stroke prevention in adult patients with non-valvular atrial fibrillation^a</p> | <p>Rivaroxaban Abdi 20mg once daily (with food) Impaired renal function with CrCl 15-49ml/min^b: Rivaroxaban Abdi 15mg once daily</p> | <p>PCI with stent placement (for max. 12 months):</p> <ul style="list-style-type: none"> • Rivaroxaban Abdi 15mg once daily (with food) plus a P2Y₁₂ inhibitor (e.g., clopidogrel) • Rivaroxaban Abdi 10mg once daily plus a P2Y₁₂ inhibitor (e.g., clopidogrel) for patients with impaired renal function (CrCl 30-49ml/min^b) |
| <p>Treatment of DVT and PE^c, and prevention of recurrent DVT and PE:</p> | | |
| <p>Adults</p> | <p>Treatment & prevention of recurrence: Day 1-21: Rivaroxaban Abdi 15mg twice daily (with food) Prevention of recurrence: Day 22 onwards: Rivaroxaban Abdi 20mg once daily (with food) Impaired renal function with CrCl 15-49ml/min^b: Rivaroxaban Abdi 15mg once daily (with food), if patient's assessed risk for bleeding outweighs risk for recurrence. Extended prevention of recurrence: After at least 6 months treatment: Rivaroxaban Abdi 10mg once daily</p> | <p>Extended prevention of recurrence in high risk patients: Rivaroxaban Abdi 20mg once daily (with food) for extended prevention of recurrence, after at least 6 months treatment, in patients at high risk of recurrent DVT or PE, such as those:</p> <ul style="list-style-type: none"> -With complicated comorbidities - Who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Abdi 10mg |
| <p>Children – dosing is based on body weight</p> | <p>For children and adolescent <18 years, Rivaroxaban Abdi treatment should be initiated following ≥5 days of initial anticoagulation treatment with parenteral heparins.</p> | |

| | | |
|--|---|--|
| | <p>The dose for children and adolescent is calculated based on body weight.</p> <p>- <u>Body weight of 50 kg or more</u>: a once daily dose of 20 mg Rivaroxaban Abdi is recommended. This is the maximum daily dose.</p> <p>- <u>Body weight from 30 to 50 kg</u>: a once daily dose of 15 mg Rivaroxaban Abdi is recommended. This is the maximum daily dose.</p> <p>- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Rivaroxaban products formulated as granules for oral suspension.</p> <p>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.</p> | |
| Prevention of VTE in adults undergoing elective hip or knee replacement surgery | <p>Rivaroxaban Abdi 10mg once daily</p> <p>Hip Replacement Surgery 5 weeks treatment duration</p> <p>Knee Replacement Surgery 2 weeks treatment duration</p> | |
| Prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischaemic events | <p>Rivaroxaban Abdi 2.5mg twice daily in combination with ASA 75-100mg/day</p> | |
| Prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers | <p>Rivaroxaban Abdi 2.5mg twice daily in combination with standard antiplatelet therapy (ASA 75-100mg/day alone or ASA 75-100mg/day plus clopidogrel 75mg/day or a standard dose of ticlopidine)</p> | |

Rivaroxaban Abdi 15mg and 20mg should be taken with food¹

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

^aWith one or more risk factors, such as congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

^bUse 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 Abdi plasma concentration.

^cNot recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

Reference: 1. Rivaroxaban Abdi 2.5 mg, 10 mg, 15 mg and 20 mg film-coated tablets: Summary of Product Characteristics

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Malta Medicines Authority ADR reporting form, which is available online at

<http://www.medicinesauthority.gov.mt/adrportal>, and sent by post or email to;

P: Pharmacovigilance Section at Post-Licensing Directorate, Malta Medicines Authority,

Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000

E: postlicensing.medicinesauthority@gov.mt

Adverse events should also be reported to AbdiPVG@apcerls.com

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