

RIVAROXABAN PINWOOD

(Rivaroxaban)

Prescriber Guide

This Prescriber Guide is not a substitute for the Rivaroxaban Pinwood Summary of Product Characteristics (SmPC). Please consult the SmPC for full prescribing information.

A digital version of the Prescriber Guide is available at the following website addresses:

www.pinewood.ie

www.hpra.ie

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

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

Ireland - Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance at www.hpra.ie.

Adverse events may also be reported to Pinewood Laboratories Ltd. Drug Safety Department (Tel: +353 52 6186000) or (email: drug.safety@pinewood.ie).

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Patient Alert Card

A Patient Alert Card is provided with the product package to each patient who is prescribed Rivaroxaban Pinewood. Please explain the implications of anticoagulant treatment to patients and/or the 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 healthcare professionals about the patient's anticoagulant treatment and will contain emergency contact information.

Please instruct patients or caregivers to carry the Patient Alert Card with them at all times and to present it to every healthcare provider, particularly if the need to have any surgery or invasive procedure. Please also instruct the patient to tick the appropriate box on the patient alert card corresponding to the dose they are taking.

Additional copies of the Patient Alert Card can be obtained by contacting Pinewood Laboratories Ltd. Medical Information by e-mail at drug.safety@pinewood.ie or by phone +353 52 6186000.

Therapeutic indication: Stroke prevention in non-valvular AF in adults

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 Pinewood 20 mg once daily*	
	TAKE WITH FOOD

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

Patients with renal impairment

In patients with moderate (creatinine clearance 30-49ml/min) or severe (15-29ml/min) renal impairment the recommended dose is 15 mg once daily. Rivaroxaban Pinewood 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 Pinewood should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Duration of therapy

Rivaroxaban Pinewood 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 treatment period.

Missed dose

If a dose is missed the patient should take Rivaroxaban Pinewood 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 percutaneous coronary intervention (PCI) with stent placement

There is limited experience of a reduced dose of 15 mg Rivaroxaban Pinewood once daily (or 10 mg Rivaroxaban Pinewood once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition to a P2Y₁₂ inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement.

Patients undergoing cardioversion

Rivaroxaban Pinewood 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 Pinewood treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation.

Oral intake

Rivaroxaban Pinewood 15 mg and 20 mg film-coated 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.

For patients who are unable to swallow whole tablets, a Rivaroxaban Pinewood 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 Pinewood 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

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

Perioperative management

If an invasive procedure or surgical intervention is required, Rivaroxaban Pinewood 15 mg and 20 mg 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 Pinewood should be assessed against the urgency of the intervention.

Rivaroxaban Pinewood 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 Pinewood in these situations.

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

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

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

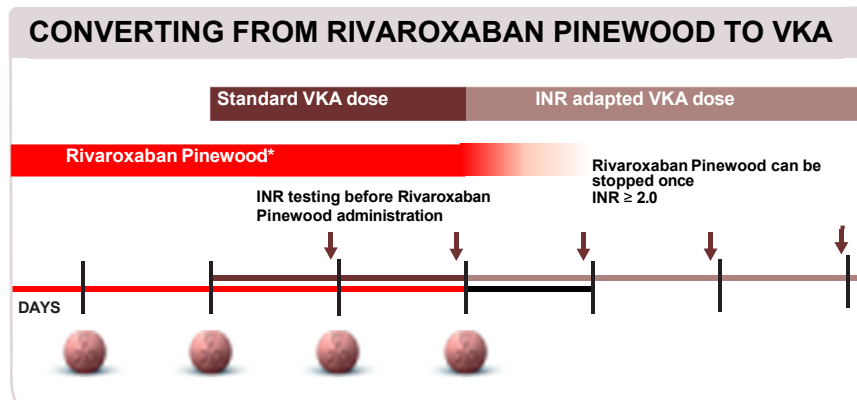
Converting from vitamin K antagonists (VKA) to Rivaroxaban Pinewood



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

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

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

Converting from parenteral anticoagulants to Rivaroxaban Pinewood

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

Converting from Rivaroxaban Pinewood to parenteral anticoagulants

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

Contraindications

Like all anticoagulants, Rivaroxaban Pinewood may increase the risk of bleeding. Therefore, Rivaroxaban Pinewood 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 Pinewood 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 Pinewood 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 treatments with Rivaroxaban Pinewood
- 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 Pinewood 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 Pinewood 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:***

The safety and efficacy of Rivaroxaban Pinewood have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban Pinewood provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Pinewood 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 Pinewood therapy.

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

Coagulation testing

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

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

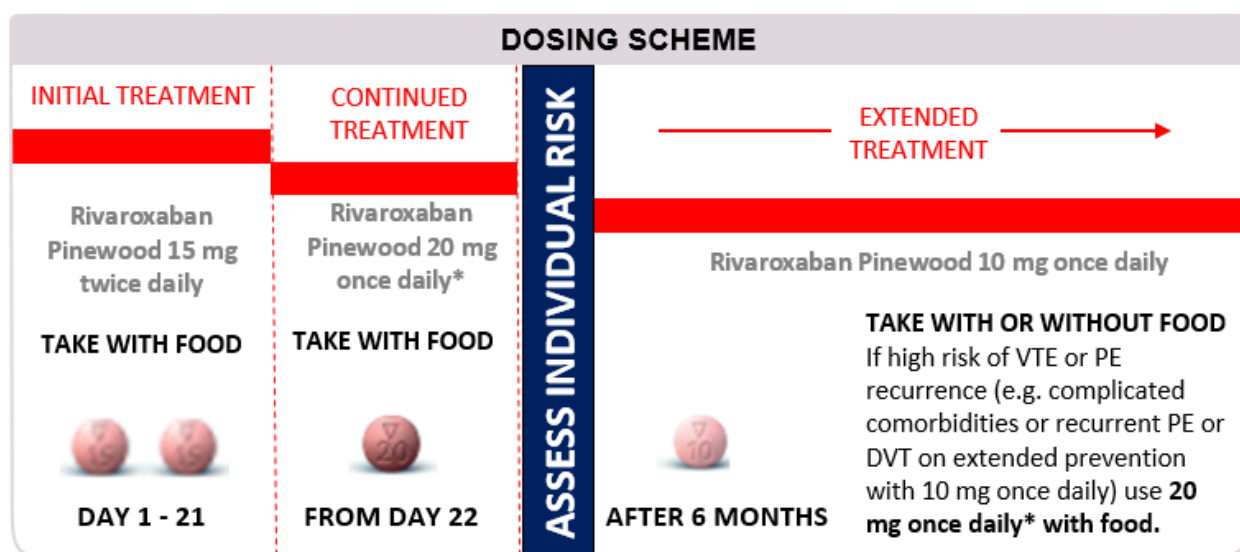
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity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

Therapeutic indication: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

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

Dosing recommendations

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



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

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg **once daily**. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Pinewood 10 mg **once daily**, a dose of Rivaroxaban Pinewood 20 mg **once daily** should be considered.

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

Patients with renal impairment

Rivaroxaban Pinewood 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 Pinewood 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 in the initial treatment phase.

However, during the continued treatment phase, a reduction of the dose from 20 mg once daily to 15 mg 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 15 mg is based on PK modelling and has not been studied in this clinical setting. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

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

Duration of therapy

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

Missed dose

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

Oral intake

Rivaroxaban Pinewood 15 mg and 20 mg film-coated 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.

For patients who are unable to swallow whole tablets, a Rivaroxaban Pinewood 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 Pinewood 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

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

Perioperative management

If an invasive procedure or surgical intervention is required, Rivaroxaban Pinewood 15 mg and 20 mg 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 Pinewood should be assessed against the urgency of the intervention.

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

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban Pinewood and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Pinewood. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Pinewood is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure. For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of Rivaroxaban Pinewood (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban Pinewood dose is administered.

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

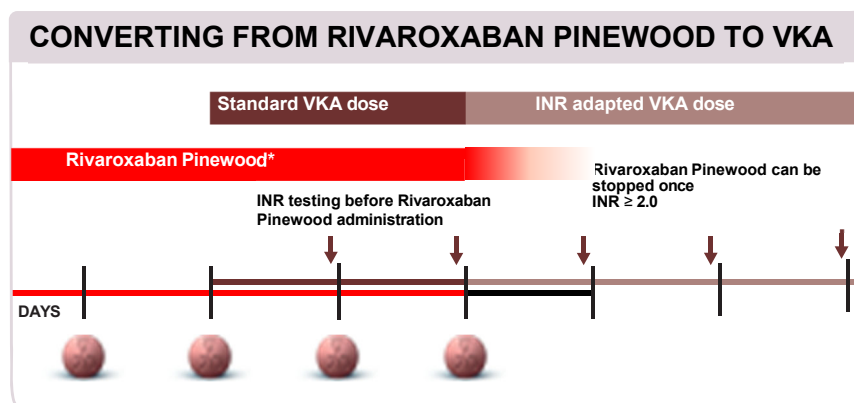
Converting from vitamin K antagonists (VKA) to Rivaroxaban Pinewood



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

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

Converting from Rivaroxaban Pinewood 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 Pinewood 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 Pinewood. While patients are on both Rivaroxaban Pinewood and VKA the **INR should not be tested earlier than 24 hours after the previous dose, but prior to the next dose of Rivaroxaban Pinewood.** Once Rivaroxaban Pinewood is discontinued, INR testing may be done reliably at least 24 hours after the last dose.

Converting from parenteral anticoagulants to Rivaroxaban Pinewood

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

Converting from Rivaroxaban Pinewood to parenteral anticoagulants

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

Contraindications

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

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

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

Coagulation testing

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

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

Therapeutic indication: Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

Dosing recommendations

The recommended dose is 10 mg Rivaroxaban Pinewood 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 DURATION	
Rivaroxaban Pinewood 10 mg once daily	
	TAKE WITH OR WITHOUT FOOD

Patients with renal impairment

Rivaroxaban Pinewood is to be used with caution in patients with severe (creatinine clearance 15-29 ml/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 50-80 ml/min) or moderate (creatinine clearance 30-49 ml/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 Pinewood 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 Pinewood 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 Pinewood 10 mg can be taken with or without food.

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

The crushed Rivaroxaban Pinewood 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 Pinewood 10 mg 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 Pinewood should be assessed against the urgency of the intervention.

Rivaroxaban Pinewood 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.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban

Pinewood and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban Pinewood. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban Pinewood is estimated to be low.

For the removal of an epidural catheter at least 18 hours should elapse after the last administration of Rivaroxaban Pinewood 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 Pinewood dose is administered.

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

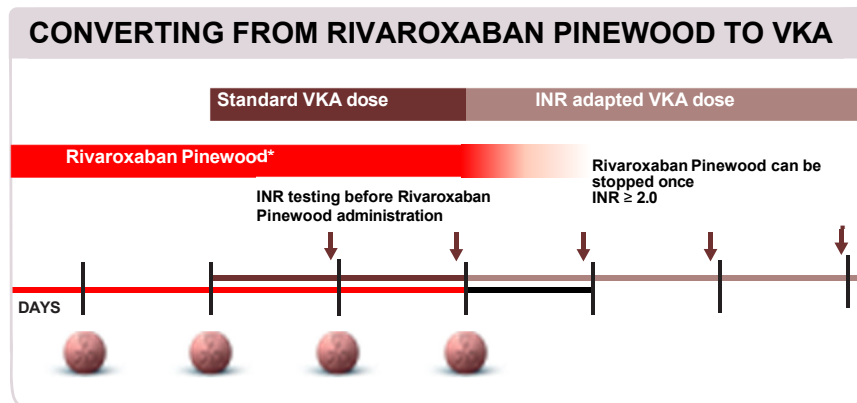
Converting from vitamin K antagonists (VKA) to Rivaroxaban Pinewood



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

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

Converting from Rivaroxaban Pinewood 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 Pinewood 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 Pinewood. While patients are on both Rivaroxaban Pinewood and VKA the **INR should not be tested earlier than 24 hours after the previous dose, but prior to the next dose of Rivaroxaban Pinewood.** Once Rivaroxaban Pinewood is discontinued, INR testing may be done reliably at least 24 hours after the last dose.

Converting from parenteral anticoagulants to Rivaroxaban Pinewood

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

Converting from Rivaroxaban Pinewood to parenteral anticoagulants

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

Contraindications

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

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

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Dosing overview table

Please consult SmPC for full product information.

Indication ^{1,2,3}	Dosing ^{1,2,3}	Special patient populations ^{1,2,3}
Stroke prevention in adult patients with non-valvular atrial fibrillation ^a	Rivaroxaban Pinewood 20 mg once daily Impaired renal function with CrCl 15-49 ml/min ^b : Rivaroxaban Pinewood 15 mg once daily	PCI with stent placement (for max. 12 months): - Rivaroxaban Pinewood 15 mg once daily plus a P2Y12 inhibitor (e.g. clopidogrel) - Rivaroxaban Pinewood 10 mg once daily plus a P2Y12 inhibitor (e.g. clopidogrel) for patients with impaired renal function (CrCl 30-49 ml/min^b)
Treatment of DVT and PE^c , and prevention of recurrent DVT and PE in adult patients	Treatment & prevention of recurrence: Day 1-21: Rivaroxaban Pinewood 15 mg twice daily Prevention of recurrence: Day 22 onwards: Rivaroxaban Pinewood 20 mg once daily Impaired renal function with CrCl 15-49 ml/min ^b : Following the initial 3 weeks of therapy with Rivaroxaban Pinewood 15 mg twice daily, Rivaroxaban Pinewood 15 mg once daily if patient's assessed risk for bleeding outweighs risk for recurrence Extended prevention of recurrence: After at least 6 months treatment: Rivaroxaban Pinewood 10 mg once daily	Extended prevention of recurrence in high risk patients: Rivaroxaban Pinewood 20 mg 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 Pinewood 10 mg

Indication ^{1,2,3}	Dosing ^{1,2,3}	Special patient populations ^{1,2,3}
Treatment of VTE , and prevention of VTE recurrence in Children and adolescents less than 18 years of age (dosing is based on body weight)	For all other children, Rivaroxaban Pinewood 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. Dose adjustments should be made based on changes in body weight only. Rivaroxaban Pinewood 15 mg and 20 mg Tablets can be used to achieve the appropriate weight-based dose. For children and adolescents weighing ≥ 30 kg and < 50 kg, use the 15 mg tablet or granules for oral suspension. For children and adolescents weighing ≥ 50 kg, use the 20 mg tablet or granules for oral suspension.	
Prevention of VTE in adults undergoing elective hip or knee replacement surgery	Rivaroxaban Pinewood 10 mg once daily Hip replacement surgery 5 weeks treatment duration Knee replacement Surgery 2 weeks treatment duration	

Rivaroxaban Pinewood 15 mg and 20 mg should be taken with food^{1,2,3}

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

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

^b Use with caution in patients with creatinine clearance 15-29 ml/min and in patients with renal

impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.

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

References

1. Rivaroxaban Pinewood 10 mg film-coated tablets Summary of Product Characteristics. Available at www.hpra.ie.
2. Rivaroxaban Pinewood 15 mg film-coated tablets Summary of Product Characteristics. Available at www.hpra.ie.
3. Rivaroxaban Pinewood 20 mg film-coated tablets Summary of Product Characteristics. Available at www.hpra.ie.