Reporting of suspected adverse reactions after the authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

NAXAT (rivaroxaban) Prescriber Guide

The Prescriber Guide provides recommendations for the use of Naxat in order to minimise the risk of bleeding during treatment with rivaroxaban. The Prescriber Guide does not substitute the Summary of Product Characteristics (SmPC) of Naxat 10mg, 15mg and 20mg film-coated tablets. Please refer to the SmPC for complete prescribing information.

This guide is provided to further minimise the risk of bleeding associated with the use of rivaroxaban, and to guide health care professionals in the management of this risk. This guide fulfils the conditions of the marketing authorisation and has been approved by the Competent Authority.

Approval Date: 10/2026

Version 1.0

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PATIENT ALERT CARD

A **Patient Alert Card** must be provided to every patient who is prescribed Naxat.

Through this Patient Alert Card, it is possible to inform physicians, including dentists, about the patient's anticoagulation treatment (rivaroxaban), and it also includes emergency contact information. The implications of anticoagulant treatment must be explained to every patient.

Please inform the patients and/or their caregivers:
- about the signs or symptoms of bleeding and when to seek medical attention
- about the importance of treatment compliance
- that the 15 mg and 20 mg film-coated tablets must be taken with food
- that the Patient Alert Card must be carried at all times and present it to every healthcare professional.
- that healthcare professionals must be informed about the patient's use of rivaroxaban in case of any surgical or invasive procedure.

THERAPEUTIC INDICATIONS

Naxat 10 mg

◆ Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

◆ Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults (see section 4.4 of the SmPC for Naxat 10 mg for haemodynamically unstable patients with PE).

Naxat 15mg & 20mg

◆ Treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults (see section 4.4 of the SmPC for Naxat 10 mg for haemodynamically unstable patients with PE).

◆ 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.

Naxat 15 mg

Pediatric population
Treatment of venous thrombosis (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least five (5) days of initial parenteral anticoagulation treatment.

Naxat 20mg

Pediatric population
Treatment of venous thrombosis (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least five (5) days of initial parenteral anticoagulation treatment.

For the full list of adverse reactions, contraindications, special warnings and precautions for use, and interactions with other medicinal products, please refer to the Summaries of Product Characteristics (SmPC) for rivaroxaban 10 mg, 15 mg, and 20 mg film-coated tablets.

Due to its pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in post-hemorrhagic anemia. The signs, symptoms, and severity (which may include fatal outcome) vary depending on the site, degree, or extent of the bleeding and/or anemia. The risk of bleeding may be increased in certain patient populations, e.g., in patients with uncontrolled severe arterial hypertension and/or concomitant medicinal products affecting haemostasis (see “Risk of bleeding” in section 4.4 of the SmPC).
Hemorrhagic complications may present as weakness, pallor, dizziness, headache, or unexplained edema, dyspnea, and unexplained shock. In some cases, as a consequence of anemia, symptoms of cardiac ischemia may occur, such as chest pain or angina. In addition, known complications secondary

to severe bleeding may occur, such as compartment syndrome or renal failure due to hypoperfusion. Therefore, when assessing the condition of any patient receiving anticoagulant therapy, the possibility of bleeding should be considered.
Clinical and laboratory monitoring is recommended in accordance with anticoagulant practice throughout the treatment period. Any unexplained fall in hemoglobin or blood pressure should prompt investigation for a bleeding source.

POPULATIONS POTENTIALLY AT HIGHER RISK OF BLEEDING

Like all anticoagulants, rivaroxaban may increase the risk of bleeding.
Patients receiving rivaroxaban should be carefully monitored for signs of bleeding throughout the treatment. In addition to adequate clinical observation, laboratory testing of hemoglobin/hematocrit may be useful for detecting occult bleeding, as appropriate.
Careful use is recommended in situations with an increased risk of bleeding. Administration of rivaroxaban should be discontinued if severe bleeding occurs.

Therefore, rivaroxaban is contraindicated in patients:

◆ with clinically significant active bleeding.

◆ with a lesion or condition, if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

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

◆ receiving concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching therapy (see section 4.2 of the SmPC) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5 of the SmPC).

Several subgroups of patients are at increased risk and should be carefully monitored for signs and symptoms of bleeding complications throughout the treatment.

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

PATIENTS WITH RENAL IMPAIRMENT

For adults, see “dosing recommendations” for patients with moderate (creatinine clearance [CrCl] 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment. Rivaroxaban is to be used with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment* who are concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations (see sections 4.4 and 4.5 of

the SmPC for each dosage form). Use of rivaroxaban is not recommended in patients with CrCl <15 ml/min.

**In children and adults with mild renal impairment (glomerular filtration rate: 50–80 ml/min/1.73 m²) no dose adjustment is required. Rivaroxaban is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 ml/min/1.73 m²).*

PATIENTS CONCOMITANTLY RECEIVING OTHER MEDICINAL PRODUCTS

- Systemic azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): use of rivaroxaban is not recommended
- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).
- 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). Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The warnings above should be taken into account also for the paediatric population.

PATIENTS WITH OTHER HAEMORRHAGIC RISK FACTORS

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

- 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

ELDERLY POPULATION

The risk of bleeding increases with increasing age.

PATIENTS WITH CANCER

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours

located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.
In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see further above).

OTHER CONTRAINDICATIONS

Rivaroxaban is contraindicated during pregnancy. Women of childbearing potential should avoid becoming pregnant during treatment with rivaroxaban. The safety and effectiveness of rivaroxaban have not been established in breastfeeding women. Animal data show that rivaroxaban is excreted in milk. Therefore, rivaroxaban is contraindicated during breastfeeding (see section 4.3 of the SmPC). A decision should be made whether to discontinue breastfeeding or to discontinue/avoid rivaroxaban treatment.
Rivaroxaban is contraindicated in cases of hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC.

PEDIATRIC POPULATION

The safety and efficacy of rivaroxaban in children aged 0 to 18 years have not been established for indications other than the treatment of venous thromboembolism (VTE) and the prevention of recurrent VTE. No data are available for other indications. Therefore, rivaroxaban is not recommended for use in children under 18 years of age for indications other than the treatment of VTE and the prevention of recurrent VTE.

DOSING RECOMMENDATION

DOSING FOR PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN ADULT PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION WITH ONE OR MORE RISK FACTORS, SUCH AS CONGESTIVE HEART FAILURE, HYPERTENSION, AGE ≥ 75 YEARS, DIABETES MELLITUS, PRIOR STROKE OR TRANSIENT ISCHAEMIC ATTACK.

The recommended dose is 20 mg once daily.

DOSING SCHEME

Continuous treatment

Rivaroxaban 20mg once daily*

TAKE WITH FOOD

*For the recommended dosing scheme in patients with atrial fibrillation and moderate or severe renal impairment, see below.

PATIENTS WITH RENAL IMPAIRMENT

In patients with moderate (creatinine clearance [CrCl] 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment the recommended dose is 15 mg once daily. Rivaroxaban is to be used with caution in patients with severe renal impairment (CrCl 15-29 ml/min). Use is not recommended in patients with creatinine clearance < 15 ml/min.
Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

DURATION OF THERAPY

Rivaroxaban should be continued long term provided the benefit of stroke prevention therapy outweighs the potential risk of bleeding.

MISSED DOSE

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

PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION UNDERGOING PCI (PERCUTANEOUS CORONARY INTERVENTION) WITH STENT PLACEMENT:

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

No data are available for corresponding patients with a history of cerebrovascular accident / transient ischemic attack (TIA).

PATIENTS UNDERGOING CARDIOVERSION

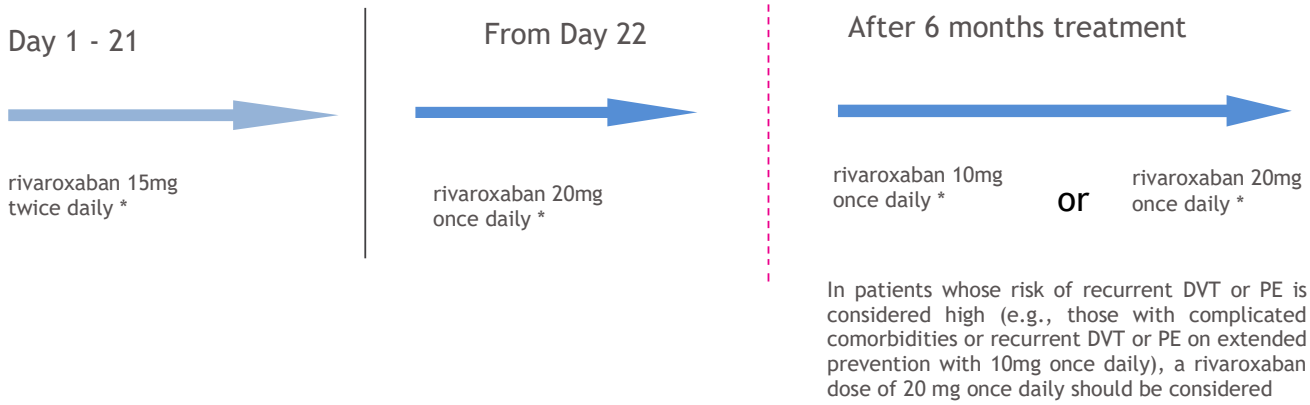
Rivaroxaban can be initiated or continued in patients who may require cardioversion.
For transoesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken rivaroxaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

DOSAGE FOR TREATMENT OF DEEP VEIN THROMBOSIS (DVT) AND PULMONARY EMBOLISM (PE), AND PREVENTION OF RECURRENT DVT AND PE

Adult patients are initially treated with 15mg twice daily for the first three weeks. This initial treatment is followed by 20 mg once daily for the continued treatment period. When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is

considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.
Rivaroxaban 10mg is **NOT** recommended for the initial 6 months treatment of DVT or PE.

DOSIG SCHEME



Rivaroxaban 10mg: TAKE WITH OR WITHOUT FOOD- Rivaroxaban 15/20mg: TAKE WITH FOOD

DOSAGE FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) AND THE PREVENTION OF RECURRENT VTE IN CHILDREN AND ADOLESCENTS

In paediatric patients and adolescents aged less than 18 years, treatment with rivaroxaban should be initiated after at least five (5) days of initial anticoagulant therapy. The dosing is based on body weight.

For children and adolescents weighing ≥30 kg, rivaroxaban (15 mg for children 30 to <50 kg / 20 mg for children ≥50 kg) once daily may be administered. The dose is determined according to body weight.

For children and adolescents weighing <30 kg, refer to the Summary of Product Characteristics for rivaroxaban oral suspension.

Table 1

Body Weight [kg]		Treatment	Total daily dose
30	< 50	15mg	15mg
≥ 50		20mg	20mg

PATIENTS WITH DVT/PE (ADULTS) – VTE (CHILDREN AND ADULTS) AND RENAL IMPAIRMENT.

ADULTS

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

Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic (PK) modelling and has not been studied in this clinical setting.

Rivaroxaban is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min. When the recommended dose is 10 mg once daily (after ≥6 months of therapy), no dose adjustment from the recommended dose is necessary.

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

CHILDREN AND ADOLESCENTS

No dose adjustment is required for children and adolescents with mild renal impairment (glomerular filtration rate: 50 ml ≤ 80 ml/min/1.73 m2), based on data in adults and limited data in paediatric patients.

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

DURATION OF THERAPY

ADULTS

Short duration of therapy with rivaroxaban (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/PE not related to major transient risk factors, unprovoked DVT/PE, or a history of recurrent DVT/PE.

CHILDREN AND ADOLESCENTS

Therapy with rivaroxaban should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis, taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

MISSED DOSE

ADULTS

- *Twice-daily treatment period (15 mg twice daily for the first 3 weeks)*

If a dose is missed, the patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this case, two 15 mg tablets may be taken at once. Continue with the regular 15 mg twice-daily intake on the following day.

- *Once-daily treatment period (beyond 3 weeks)*

If a dose is missed, the patient should take rivaroxaban immediately and continue on the following day with the once-daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

CHILDREN AND ADOLESCENTS

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.

DOSAGE FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) IN ADULTS PATIENTS UNDERGOING ELECTIVE HIP OR KNEE REPLACEMENT SURGERY

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

DURATION OF THERAPY

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

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

MISSED DOSE

If a dose is missed the patient should take rivaroxaban immediately and then continue the following day with once daily intake as before.

ORAL INTAKE

Rivaroxaban 10mg can be taken with or without food.
Rivaroxaban 15mg and 20mg are to be taken with food. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

ADULTS

For patients who are unable to swallow whole tablets:

- tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed rivaroxaban 15 mg or 20 mg film-coated tablets/capsules, the dose should then be immediately followed by enteral feeding (see section 5.2 of SmPC).

CHILDREN AND ADOLESCENTS

For children weighing 30-50 kg who are unable to swallow whole tablets, other rivaroxaban-containing

products granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of rivaroxaban 15 mg or 20 mg are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet or springling capsules and mixing it with water or apple purée immediately prior to use and administered orally.

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

PERIOPERATIVE MANAGEMENT

If an invasive procedure or surgical intervention is required, if possible and based on the clinical judgement of the physician, rivaroxaban 10/15/20 mg should be stopped at least 24 hours before the intervention.

If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.

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

SPINAL/EPIDURAL ANAESTHESIA OR PUNCTURE

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma, which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Indication-specific recommendations:

- PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION WITH ONE OR MORE RISK FACTORS

- TREATMENT OF DVT AND PE AND PREVENTION OF RECURRENT DVT AND PE IN ADULT PATIENTS

- TREATMENT OF VTE AND PREVENTION OF VTE RECURRENCE IN CHILDREN

There is no clinical experience with the use of 15 mg and 20 mg rivaroxaban tablets/capsules in adults nor with the use of rivaroxaban in children in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

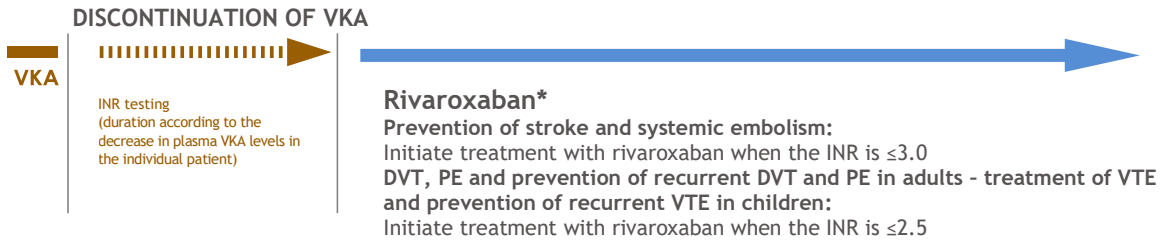
For the removal of an epidural catheter and based on the general pharmacokinetic characteristics, at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients, should elapse after the last administration of rivaroxaban (see section 5.2 of the SmPC of rivaroxaban 15mg & 20mg). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs, the administration of rivaroxaban is to be delayed for 24 hours.
No data is available on the timing of the placement or removal of a neuraxial catheter in children while on rivaroxaban. Discontinue rivaroxaban and consider a short-acting parenteral anticoagulant.

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

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2 of the SmPC).
At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs, the administration of rivaroxaban is to be delayed for 24 hours.

CONVERTING FROM VITAMIN K ANTAGONISTS (VKA) TO RIVAROXABAN

CONVERTING FROM VKA TO RIVAROXABAN



* See dosing recommendations for the required daily dose

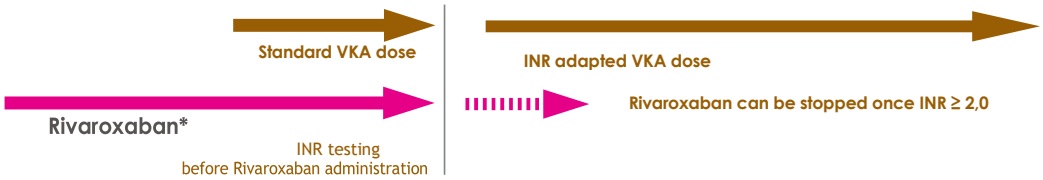
For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and rivaroxaban therapy should be initiated when the **INR ≤3.0.**

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

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

CONVERTING FROM RIVAROXABAN TO VITAMIN K ANTAGONISTS (VKA)

CONVERTING FROM RIVAROXABAN TO VKA



*See dosing recommendation for required daily dose.

ADULTS

When converting to VKA, rivaroxaban and VKA should be given concurrently until the **INR is ≥ 2.0**. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of rivaroxaban. While patients are on both rivaroxaban and VKA the **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban**. Once rivaroxaban is discontinued, INR values obtained at least 24 hours after the last dose reliably reflect the VKA dosing.

CHILDREN

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

CONVERTING FROM PARENTERAL ANTICOAGULANTS TO RIVAROXABAN

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

CONVERTING FROM RIVAROXABAN TO PARENTERAL ANTICOAGULANTS

Give the first dose of the parenteral anticoagulant at the time the next rivaroxaban dose would have been taken.

OVERDOSE

Due to limited absorption, a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban and above in adults; however, no data is available at supratherapeutic doses in children.

A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa); however, it is not established in children. The use of activated charcoal to reduce absorption in case of overdose may be considered.

BLEEDING MANAGEMENT

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment discontinued as appropriate.
Individualised bleeding management may include:

- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Haemodynamic support, blood product or component transfusion
- If bleeding cannot be controlled with the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (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.

Depending on local availability, consultation with a physician experienced in coagulation disorders should be considered in cases of severe bleeding.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

COAGULATION TESTING

Rivaroxaban does not require routine coagulation monitoring. However, measuring rivaroxaban levels may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to make clinical decisions, e.g. overdose and emergency surgery.
Anti-FXa assays with rivaroxaban specific calibrators to measure rivaroxaban levels are now commercially available (see section 5.1 of the SmPC). If clinically indicated haemostatic status can also be assessed by PT using Neoplastin as described in the SmPC.
The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin

time (aPTT) and calculated PT international normalised ratio (INR). Since the INR was developed to assess the effects of VKAs on the PT, it is therefore not appropriate to use the INR to measure activity of rivaroxaban.
Dosing or treatment decisions should not be based on results of INR except when converting from rivaroxaban to VKA as described above.

DOSING OVERVIEW TABLE IN ADULTS*

**For dosing for the treatment of VTE and the prevention of recurrent VTE in paediatric patients, refer to Table 1 on page 10*

INDICATION	DOSING	SPECIAL PATIENT POPULATION
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation[a] with one or more risk factors	**Rivaroxaban 20 mg once daily**	Impaired renal function with CrCl 15-49ml/min[b]: **Rivaroxaban 15mg once daily** PCI with stent placement For maximun 12 months: **Rivaroxaban 15mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel) PCI with stent placement in patients with impaired renal function CrCl 30-49ml/min[b]: **Rivaroxaban 10mg once daily** plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel)
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)[c] and prevention of recurrent DVT and PE in adults	Treatment & prevention of recurrence: Day 1-21: **Rivaroxaban 15 mg twice daily** Prevention of recurrence: Day 22 onwards: **Rivaroxaban 20 mg once daily** Extended prevention of recurrence: from month 7 onwards: **Rivaroxaban 10 mg once daily** Extended prevention of recurrence: from month 7 onwards: **Rivaroxaban 20 mg once daily** in patients at high risk of recurrent DVT or PE, such as those: • With complicated comorbidities • Who have developed recurrent DVT or PE on extended prevention with Rivaroxaban 10 mg once daily	Impaired renal function with CrCl 15-49ml/min[b]: Treatment & prevention of recurrence: Day 1-21: **Rivaroxaban 15 mg twice daily** Thereafter, **Rivaroxaban 15 mg once daily** instead of Rivaroxaban 20 mg once daily, if patient's assessed risk for bleeding outweighs risk for recurrence. When the recommended dose is Rivaroxaban 10 mg once daily, no dose adjustment is necessary.
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	Rivaroxaban 10 mg once daily	

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

b. Use with caution in patients with creatinine clearance 15-29ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration.

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

Rivaroxaban 15 mg and 20 mg should be taken with food

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

CALL FOR REPORTING OF SUSPECTED ADVERSE DRUG REACTIONS

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

Alternatively, adverse reactions may also be reported to Delorbis Pharmaceuticals Ltd, at the following contact details:

Tel: +357 97 77 35 71
Email: drugsafety@delorbispharma.eu

WHERE TO FIND FURTHER INFORMATION

For further information, refer to the Summary of Product Characteristics (SmPC) for NAXAT or contact the Medical Information Department of Delorbis Pharmaceuticals Ltd at: +357 22 845000

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NOTES: