RIVAROXABAN ROWEX 10MG, 15MG & 20MG FILM-COATED TABLETS - PA0711/275/001-003

PRESCRIBER GUIDE

Patient Alert Card

A patient alert card must be provided to each patient who is prescribed rivaroxaban 10, 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance, the need to take with food and signs of bleeding and when to seek medical attention should be discussed with the patient.

The patient alert card will inform physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every health care provider, especially if they need to have surgery or other invasive procedures.

Dosing Recommendations

Dosing in patients with atrial fibrillation

For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 20 mg once daily.

Patients with renal impairment:
In patient with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29 ml/min) renal impairment the recommended dose is 15 mg once daily. Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 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 who undergo 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.

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.

Dosing in treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults

Patients are initially treated with 15 mg twice daily for the first 3 weeks. This initial treatment is followed by 20 mg once daily for the continued treatment period.

	Dosing schedule	Maximum daily dose
Day 1 – 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily*	20 mg

*Patients with DVT/PE and renal impairment

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 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 PK modelling and has not been studied in this clinical setting.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 mL/min). The use of Rivaroxaban is not recommended in patients with creatinine clearance < 15 mL/min. Rivaroxaban should be used

Rivaroxaban Rowex Prescriber guide.indd 1 22/06/2018 08:50

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

Duration of therapy: The duration of therapy should be individualized after assessment of the treatment benefit against the risk of bleeding. Missed dose:

- twice daily treatment period (15 mg bid for the first three weeks):
  If a dose is missed, the patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
- once daily treatment period (beyond three weeks):
  If a dose is missed, the patient should take rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

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

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

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.

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 10 mg:

Rivaroxaban 10 mg can be taken with or without food.

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

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.

Rivaroxaban 15 mg and 20 mg:

Rivaroxaban 15 mg and 20 mg 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, rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and 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, the dose should then be immediately followed by enteral feeding.

Perioperative Management

If an invasive procedure or surgical intervention is required, rivaroxaban 10 mg, 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 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 postoperative 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. For indication specific recommendations please refer to the sections below:

Rivaroxaban Rowex Prescriber guide.indd 2 22/06/2018 08:50

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF) Treatment of DVT and PE and prevention of recurrent DVT and PE in adults
There is no clinical experience with the use of 15/20 mg rivaroxaban in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2 of the SmPC). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Converting from Vitamin K Antagonists (VKA) to Rivaroxaban
For patients treated for prevention of stroke and systemic embolism, treatment with Vitamin K Antagonists (VKA) should be stopped and rivaroxaban therapy should be initiated when the INR is ≤ 3.0.

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

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

Converting from Rivaroxaban to Vitamin K Antagonists (VKA)
It is important to ensure adequate anticoagulation while minimizing the risk of bleeding during conversion of therapy.

When converting from rivaroxaban to VKA, rivaroxaban and VKA should be given overlapping 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, as 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 testing may be done reliably at least 24 hours after the last dose reliably reflect the VKA dosing.

Converting from Parenteral Anticoagulants to Rivaroxaban
- Patients with continuously administered parenteral medicinal product such as intravenous unfractionated heparin: Start rivaroxaban at the time of discontinuation.
- Patients with parenteral medicinal product on a fixed dosing scheme such as LMWH: Discontinue parenteral medicinal product and start rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product.

Converting from Rivaroxaban to Parenteral Anticoagulants
The first dose of parenteral anticoagulant should be given at the time that the next rivaroxaban dose would have been due.

Populations Potentially at Higher Risk of Bleeding
Like all anticoagulants, Rivaroxaban may increase the risk of bleeding.
Therefore Rivaroxaban is contraindicated in patients
- with active clinically significant bleeding
- with a lesion or condition at significant risk for major bleeding such as 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 esophageal 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, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy to or from rivaroxaban or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

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 initiaton of treatment (see section 4.4 and 4.8 of the relevant SmPC). 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 for bleeding:
- In patients with moderate renal impairment (creatine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations rivaroxaban is to be used with caution.

Rivaroxaban Rowex Prescriber guide.indd 3 22/06/2018 08:50

- Patients with renal impairment: See "dosing recommendations" for patients with moderate (creatinine clearance 30 - 49 mL/min) or severe (15 - 29 mL/min) renal impairment. Rivaroxaban is to be used with caution in patients with creatinine clearance (15 - 29 mL/min) and in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations. Use of Rivaroxaban is not recommended in patients with creatinine clearance <15 mL/min.
- 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 NSAIDs, acetylsalicylic acid or platelet aggregation inhibitors. After an acute coronary syndrome patients on treatment with Rivaroxaban and ASA or Rivaroxaban and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- Patients with other haemorrhagic risk factors

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

Other contraindications
Rivaroxaban is contraindicated during pregnancy and breast-feeding. Women of childbearing potential should avoid becoming pregnant during treatment with Rivaroxaban.

Rivaroxaban is also contraindicated in case of hypersensitivity to the active substance or to any of the excipients.

Overdose
Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg Rivaroxaban and above. The use of activated charcoal to reduce absorption in case of overdose may be considered.

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

Individualized bleeding management may include
- Symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- Haemodynamic support, blood product or component transfusion
- For life-threatening bleeding that cannot be controlled with the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban.

Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable.

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 take clinical decisions, e.g. overdose and emergency surgery.

Anti-FXa assays with rivaroxaban-specific calibrators to measure rivaroxaban levels are now commercially available. If clinically indicated, haemostatic status can also be assessed by Prothrombin time 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 normalized 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 the 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.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Rivaroxaban Rowex Prescriber guide.indd 4 22/06/2018 08:50

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