Rivaroxaban QO®
(Rivaroxaban)
Prescriber Guide

This document is approved by The Executive Directorate of Pharmacovigilance at SFDA

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Prescriber Guide

The Prescriber Guide provides recommendations for the use of Rivaroxaban QO® in order to minimise the risk of bleeding during treatment with Rivaroxaban QO. The Prescriber Guide does not substitute the Rivaroxaban QO Summary of Product Characteristics (SmPC) before prescribing please also read the Rivaroxaban QO SmPC.

Patient Alert Card

A patient alert card must be provided to each patient who is prescribed Rivaroxaban QO.The implications of anticoagulant treatment should be explained the importance of compliance, signs of bleeding and when to seek medical attention discussed with the patient or the caregiver.

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 healthcare provider.

Dosing recommendations

Stroke prevention in adult patients with non-valvular atrial fibrillation

The recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF) is 20 mg once daily.

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 QO' 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 < 15ml/min.

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

Duration of therapy

Rivaroxaban QO 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 QO' immediately and continue on the following day with the once-daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Patients with non-valvular atrial fibrillation undergoing PCI with stent placement

There is limited experience of a reduced dose of 15 mg 'Rivaroxaban QO' once daily (or 10 mg 'Rivaroxaban QO' 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 QO' 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 QO' 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 QO' as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adult patients

Patients are initially treated with Rivaroxaban QO 15 mg twice daily for the first 3 weeks. This initial treatment is followed by 'Rivaroxaban QO' 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 QO 10 mg once daily, a dose of 'Rivaroxaban QO' 20 mg once daily should be considered. 'Rivaroxaban QO' 10 mg is not recommended for the initial 6 months' treatment of DVT or PE.

*Rivaroxaban QO take with or without food, Rivaroxaban QO 15 and 20mg must be taken with food.

Patients with renal impairment

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

Thereafter, the recommended dose is 'Rivaroxaban QO' 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 of bleeding outweighs the risk of 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 QO' 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 < 15ml/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 QO' should be used with caution in patients with renal impairment concomitantly

receiving other medicinal products that increase Rivaroxaban QO plasma concentrations.

Duration of therapy

Short duration of therapy (≥3 months) should be considered in patients with DVT/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.

Missed dose

Twice-daily treatment period (15 mg twice daily for the first 3 weeks) If a dose is missed, the patient should take 'Rivaroxaban QO' immediately to ensure intake of 30 mg 'Rivaroxaban QO' 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 QO' 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 atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

Patients taking 'Rivaroxaban' 2.5 mg twice daily should also take a daily dose of 75-100 mg acetylsalicylic acid (ASA). In patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, treatment should not be started until haemostasis is achieved.

Patients with renal impairment

No dose adjustment is required in patients with moderate renal impairment (CrCl 30–49 ml/min). '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 <15ml/min.
In patients with moderate renal impairment (CrCl 30–49 ml/min) concomitantly receiving other medicinal products that increase Rivaroxaban QO plasma concentrations, 'Rivaroxaban' is to be used with caution.

Duration of therapy

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

Co-administration with antiplatelet therapy

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of Rivaroxaban 2.5 mg twice daily should be evaluated depending on

the type of event or procedure and antiplatelet regimen.

Other warnings and precautions in CAD/PAD patients

In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of Rivaroxaban 2.5 mg twice daily have been investigated in combination with ASA.

In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Rivaroxaban QO 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided Patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months.
Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

Concomitant treatment of CAD/PAD with 'Rivaroxaban' 2.5 mg twice daily and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month. Treatment with Rivaroxaban 2.5 mg should be avoided in patients with previous stroke or TIA receiving dual antiplatelet therapy.
'Rivaroxaban QO' co-administered with ASA should be used with caution in CAD/PAD patients:

- ≥ 75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis
- With a lower weight (<60mg)
- In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with Rivaroxaban QO.

'Rivaroxaban' Missed dose

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

Prevention of VTE in adult patients undergoing elective hipor knee-replacement surgery

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

Duration of treatment

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 QO' immediately and then continue the following day with once-daily intake as before.

Oral intake

Rivaroxaban QO 10 mg can be taken with or without food. Rivaroxaban QO 15 mg and 20 mg 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. For patients who are unable to swallow whole tablets, a Rivaroxaban QO 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 QO 15 mg or 20 mg filmcoated tablets, the dose should be immediately followed by food. The crushed Rivaroxaban QO 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 QO 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: if possible and based on the clinical judgement of the physician:
Rivaroxaban QO 10/15/20 mg should be stopped at least 24 hours before the intervention
Rivaroxaban QO 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 adult patients with NVAF /
- Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients

There is no clinical experience with the use of 15 mg and 20 mg Rivaroxaban QO® in these situations. To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban QO and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban QO. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban QO 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 patients and 26 hours in elderly patients should elapse after the last administration of Rivaroxaban QO. Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban QO dose is administered. If traumatic puncture occurs, the administration of is Rivaroxaban QOto be delayed for 24 hours.

- 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 QO and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban QO.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban QO is estimated to be low.

At least 18 hours should elapse after the last administration of Rivaroxaban QO before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next Rivaroxaban QO dose is administered. If traumatic puncture occurs the administration of Rivaroxaban QO is to be delayed for 24 hours.

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

There is no clinical experience with the use of 2.5 mg and antiplatelet agents alone in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

To reduce the potential risk of bleeding associated with the concurrent use of Rivaroxaban QO and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Rivaroxaban QO.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rivaroxaban QO is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Converting from VKA to Rivaroxaban QO

For patients treated for prevention of stroke and systemic embolism, treatment with VKA should be stopped and Rivaroxaban QO therapy should be initiated when the International Normalised Ratio (INR ≤3.0).

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

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

Converting from Rivaroxaban QO to VKA

It is important to ensure adequate anticoagulation while minimising the risk of bleeding during conversion of therapy. When converting to VKA, Rivaroxaban QO and VKA should be given concurrently until the **INR ≥2.0**. For the first 2 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 QO**. While patients are on both 'Rivaroxaban QO' and VKA the **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban QO**. Once 'Rivaroxaban QO' is discontinued, INR values obtained at least 24 hours after the last dose reliably reflect the VKA dosing.

Converting from parenteral anticoagulants to Rivaroxaban QO

- Patients with a parenteral drug on a fixed dosing scheme such as lowmolecular-weight heparin (LMWH): Discontinue parenteral drug and start 'Rivaroxaban QO' 0 to 2 hours before the time of the next scheduled administration of the parenteral drug
- Patients with a continuously administered parenteral drug such as intravenous unfractionated heparin: Start 'Rivaroxaban QO' at the time of discontinuation

Converting from Rivaroxaban QO to parenteral anticoagulants

Give the first dose of the parenteral anticoagulant at the time the next 'Rivaroxaban QO' dose

would be taken.

Populations potentially at higher risk of bleeding

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

- With active clinically significant bleeding
- With a lesion or condition, if considered to be a significant risk for 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), LMWHs (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under the circumstances of switching anticoagulant therapy 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 ChildPugh class B and C cirrhotic patients.

Elderly population: The risk of bleeding increases with increasing age.
Several subgroups of patients are at increased risk and should be carefully monitored for signs and symptoms of bleeding complications.
Treatment decision in these patients should be carried out after assessment of treatment benefit against the risk for bleeding.

Patients with renal impairment

See dosing recommendations for patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment. Rivaroxaban QO is to be used with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment (CrCl concomitantly receiving other medicinal products that increase Rivaroxaban QO plasma concentrations. Use of Rivaroxaban QO is not recommended in patients with CrCl < 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 QO is not recommended
- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)

- CAD/PAD patients: Patients on treatment with Rivaroxaban QO and antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (For patients with renal impairment see further above).

Patients with other haemorrhagic risk factors

As with other antithrombotics, Rivaroxaban QO' 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 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 QO therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of Rivaroxaban QO is contraindicated (see further above).

Other contraindications

Rivaroxaban QO is contraindicated during pregnancy and breastfeeding. Women of childbearing potential should avoid becoming pregnant during treatment with Rivaroxaban QO. Rivaroxaban QO 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 QO and above. A specific reversal agent antagonising the pharmacodynamic effect of Rivaroxaban QO is available (refer to the Summary of Product Characteristics of andexanet alfa). 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 QO, the next Rivaroxaban QO 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
- Haemodynamic support, blood product or component transfusion
- If bleeding cannot be controlled with the above measures, either 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 individuals receiving Rivaroxaban QO.

Due to the high plasma protein binding, Rivaroxaban QO is not expected to be dialysable.

Coagulation Testing

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

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

The following coagulation tests are increased: PT, activated partial thromboplastin time (aPTT) and calculated PT 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 QO.

Dosing or treatment decisions should not be based on results of INR except when converting from Rivaroxaban QO to VKA as described above.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; CAD, coronary artery disease; CrCl, creatinine clearance; DVT, deep vein thrombosis; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; INR, international normalised ratio; LMWH, low-molecular-weight heparin; NSAID, non-steroidal anti-inflammatory drug; NVAF, non-valvular atrial fibrillation; OD, once daily; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; SmPC, Summary of Product Characteristics; SPAF, stroke prevention in atrial fibrillation; TID, three times daily; VKA, vitamin K antagonist; VTE, venous thromboembolism; UFH, unfractionated heparin.

This medicinal product is subject to additional monitoring. This will allow quick identification of

new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Reporting:
The treating healthcare physicians are advised to report adverse events in accordance with the national spontaneous reporting system.

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Should you have any questions, please do not hesitate to contact us. We will keep you informed as further information becomes available.