Xarelto®
rivaroxaban

Prescriber Guide
Version 7

BAYER

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Patient Alert Card

A patient alert card must be provided to each patient who is prescribed Xarelto® 2.5 mg, 10 mg, 15 mg or 20 mg and is provided with the product package. The implications of anticoagulant treatment should be explained. Specifically, the need for compliance 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.

Dosing Recommendations

Dosing in patients with atrial fibrillation

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

DOSING SCHEME

CONTINUOUS TREATMENT

Xarelto® 20 mg once daily*

TAKE WITH FOOD

*Patients with renal impairment

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (15 – 29ml/min) renal impairment the recommended dose is 15 mg once daily. Xarelto® is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and is not recommended in patients with creatinine clearance <15 ml/min.

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

Duration of therapy

Xarelto® 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 Xarelto® 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 Xarelto® once daily (or 10 mg Xarelto® 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

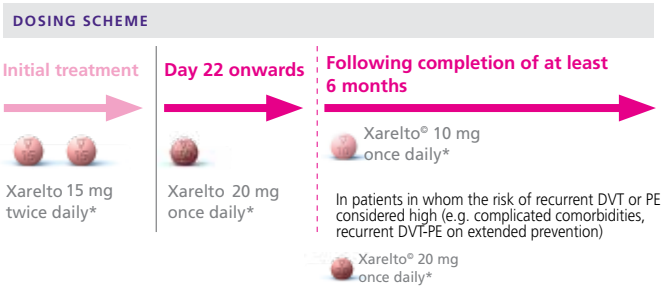
Xarelto® can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Xarelto® treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken Xarelto® 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) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults

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.

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 Xarelto® 10 mg **once daily**, a dose of Xarelto® 20 mg **once daily** should be considered.

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



*Recommended dosing scheme for patients with DVT/PE and moderate or severe renal impairment see below

10mg: take with or without food
15/20mg: must be taken with food

*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. Xarelto® is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and is not recommended in patients with creatinine clearance <15 ml/min. When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

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 Xarelto® immediately to ensure intake of 30 mg Xarelto® 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 Xarelto® 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 after an acute coronary syndrome (ACS) with elevated cardiac biomarkers

DOSING SCHEME

INIVIDUAL TREATMENT DURATION

Xarelto® 2.5 mg twice daily*

TAKE WITH FOOD

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

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

In addition to Xarelto® 2.5 mg, patients should also take a daily dose of 75 - 100 mg ASA or a daily dose of 75 - 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine. Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

Patients with renal impairment

No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min). Xarelto® is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and is not recommended in patients with creatinine clearance <15 ml/min.

In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Xarelto® is to be used with caution.

Duration of therapy

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

Other warnings and precautions in ACS patients

Xarelto® should be used with caution in ACS patients

- >75 years of age if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine
- with a low weight (<60 kg) if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine

Concomitant treatment of ACS with Xarelto® and antiplatelet therapy is contraindicated in patients with a prior stroke or a transient ischaemic attack (TIA).

Missed dose

If a dose is missed the patient should continue with the regular 2.5 mg Xarelto® 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 hip or knee replacement surgery

The recommended dose is 10 mg Xarelto® 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 Xarelto® immediately and then continue the following day with once daily intake as before.

Oral Intake

Xarelto® 2.5 mg and 10mg can be taken with or without food. Xarelto® 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, a Xarelto® tablet may be crushed and mixed with water or apple puree immediately prior to use and then administered orally. After the administration of crushed Xarelto® 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed Xarelto® 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 Xarelto® 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,

- Xarelto® 10/15/20 mg should be stopped at least 24 hours before the intervention
- Xarelto® 2.5 mg should be stopped at least 12 hours before the intervention

If possible and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto® should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate Hemostasis 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.

For indication specific recommendations please refer to the sections below:

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

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

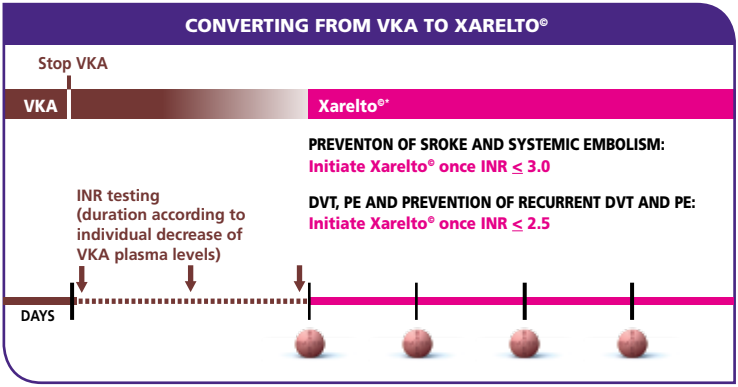
There is no clinical experience with the use of 10/15/20 mg Xarelto® in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement 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 SPC). 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.

Prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers

There is no clinical experience with the use of 2.5 mg Xarelto® with ASA alone or with ASA plus clopidogrel or ticlopidine 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 (see section 5.2 of the SPC). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

Converting from VKA to Xarelto©



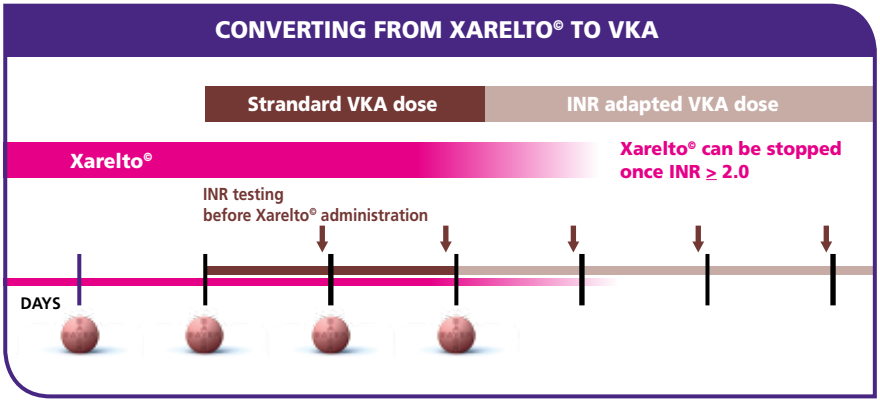
*See dosing recommendations for required daily dose

For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and Xarelto® 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 Xarelto® therapy should be initiated when the **INR ≤2.5**.

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

Converting from Xarelto© 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, Xarelto® and VKA should be given overlapping until the **INR ≥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 Xarelto®. While patients are on both Xarelto® and VKA the **INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto®**. Once Xarelto® is discontinued, INR values obtained at least 24 hours after the last dose reliably reflect the VKA dosing.

Converting from Parenteral Anticoagulants to Xarelto®

- Patients with continuously administered parenteral drug such as intravenous unfractionated heparin: Start Xarelto® at the time of discontinuation.
- Patients with parenteral drug on a fixed dosing scheme such as LMWH: Discontinue parenteral drug and start Xarelto® 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

Converting from Xarelto® to Parenteral Anticoagulants

Give the first dose of the parenteral anticoagulant at the time the next Xarelto® dose would be taken.

Populations Potentially at Higher Risk of Bleeding

Like all anticoagulants, Xarelto® may increase the risk of bleeding.

Therefore Xarelto® 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), low molecular weight heparins (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 Child-Pugh class B and C cirrhotic patients

Several sub-groups 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 done after assessment of treatment benefit against the risk for bleeding.

- **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. Xarelto® 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 Xarelto® 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 Xarelto® is not recommended
  - Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
  - After an acute coronary syndrome patients on treatment with Xarelto® and ASA or Xarelto® and ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk

- **Patients with other Hemorrhagic risk factors. As with other antithrombotics, Xarelto® 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

Other contraindications

Xarelto® is contraindicated during pregnancy and breast feeding. Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto®. Xarelto® 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 Xarelto® 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 Xarelto®, the next Xarelto® 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
- Hemodynamic 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 Xarelto®.

Due to the high plasma protein binding Xarelto® is not expected to be dialysable.

Coagulation Testing

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

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

The following coagulation tests are increased: Prothrombin time (PT), activated partial thromboplastin time (aPTT) and calculated PT international 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 activity of Xarelto®.

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

▼ 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.

Suspected adverse reactions and medication errors should be reported. Report forms can be downloaded from: **www.medicinesauthority.gov.mt/adrportal** and sent to **postlicensing.medicinesauthority@gov.mt** or **pv@alfredgera.com**

▼ Xarelto® 10, 15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 10mg/15mg/20mg rivaroxaban tablet **Indication(s):** *10mg* Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults. *15mg/20mg* Prevention of stroke & systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors such as congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke or transient ischaemic attack (SPAF). Treatment of DVT & PE, & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *10mg* - *hip or knee replacement surgery:* oral *o.d.* dose; initial dose taken 6 to 10 hours after surgery provided haemostasis established. *DVT & PE:* 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 *o.d.*. 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 Xarelto 10 mg *o.d.*, a dose of Xarelto 20 mg *o.d.* should be considered. *15mg/20mg* – Take with food *SPAF:* 20 mg orally *o.d. DVT & PE:* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.*. *10mg/15mg/20mg* - Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. ***Special populations:*** Patients undergoing cardioversion: Xarelto can be initiated or continued in patients who may require cardioversion. 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 Xarelto once daily (or 10 mg Xarelto 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 & undergo PCI with stent placement. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment; *10mg* - moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. Severe (creatinine clearance 15-29ml/min) - limited data indicate concentrations are significantly increased, use with caution. *15mg/20mg* - moderate & severe renal impairement - limited data indicates plasma concentrations are significantly increased, use with caution – *SPAF:* reduce dose to 15mg *o.d.*, *DVT & PE:* 15 mg *b.i.d.* for 3 weeks, thereafter 20mg *o.d.* Consider reduction from 20mg to 15mg *o.d.* if patient's bleeding risk outweighs risk for recurrent DVT & PE; *–All strengths* - Creatinine clearance <15 ml/min - not recommended. ***Hepatic impairment:*** Do not use in patients with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C ***Paediatrics:*** Not recommended. **Contra-indications:** Hypersensitivity to active substance or any excipient; active clinically significant bleeding; lesion or condition considered to confer a significant risk for major bleeding (refer to SmPC); concomitant treatment with any other anticoagulants except under specific circumstances of switching anticoagulant therapy or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter; hepatic disease associated with coagulopathy & clinically relevant bleeding risk including cirrhotic patients with Child Pugh B & C; pregnancy & breast feeding. **Warnings & precautions (W&P):** Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. Increasing age may increase haemorrhagic risk. Xarelto should be discontinued at the first appearance of a severe skin rash, or any other sign of hypersensitivity in conjunction with mucosal lesions. *Not recommended:* in patients with an increased bleeding risk (refer to SmPC); in patients receiving concomitant systemic treatment with strong CYP3A4 & P-gp inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; in patients with prosthetic heart valves; in haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy. *Use with caution:* in patients with severe renal impairment or with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicinal products affecting haemostatis; when neuraxial anaesthesia or spinal/epidural puncture is employed; in patients at risk of ulcerative gastrointestinal disease (prophylactic treatment may be considered). If invasive procedures or surgical intervention are required stop Xarelto use at least 24 hours beforehand. Restart use as soon as possible provided adequate haemostasis has been established.There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests. Xarelto contains lactose. **Interactions:** Concomitant use with strong inhibitors of both CYP3A4 & P-gp not recommended as clinically relevant increased rivaroxaban plasma concentrations are observed. Avoid co-administration with dronedarone. Use with caution in patients concomitantly receiving NSAIDs, acetylsalicylic acid (ASA) or platelet aggregation inhibitors due to the increased bleeding risk; use with caution in patients concomitantly receiving SSRIs/SNRIs due to a possible increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs & symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive & use machines:** syncope (uncommon) & dizziness (common) were reported. Patients experiencing these effects should not drive or use machines. **Undesirable effects:** *Common:* anaemia, dizziness, headache, eye haemorrhage, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, GI tract haemorrhage, GI & abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting, pruritus, rash, ecchymosis, cutaneous & subcutaneous haemorrhage, pain in extremity, urogenital tract haemorrhage (menorrhagia *very common* in women <55 yrs treated for DVT, PE & prevention of recurrence), renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings & Precautions – in addition:* thrombocytosis, thrombocytopenia, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, angioedema & allergic oedema, occult bleeding/haemorrhage from any tissue (e.g. cerebral & intracranial, haemarthrosis, muscle) which may lead to complications (incl. compartment syndrome, renal failure, fatal outcome), syncope, tachycardia, hepatic impairment, cholestasis & hepatitis (incl. hepatocellular injury), hyperbilirubinaemia, jaundice, vascular pseudoaneurysm following percutaneous vascular intervention. Prescribers should consult SmPC in relation to full side effect information. **Overdose:** No specific antidote is available. **Legal Category:** POM. **MA Number(s):** *10mg* - EU/1/08/472/001-10, 022, 042-045 *15mg/20mg* - EU/1/08/472/011-21, 023-024, 036-037, 040 **Date of preparation:** November 2017.

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