Xarelto®(rivaroxaban) Prescriber Guide

Xarelto®
ivaroxaban

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. See final page of this booklet on how to report adverse events.

Patient Alert Card

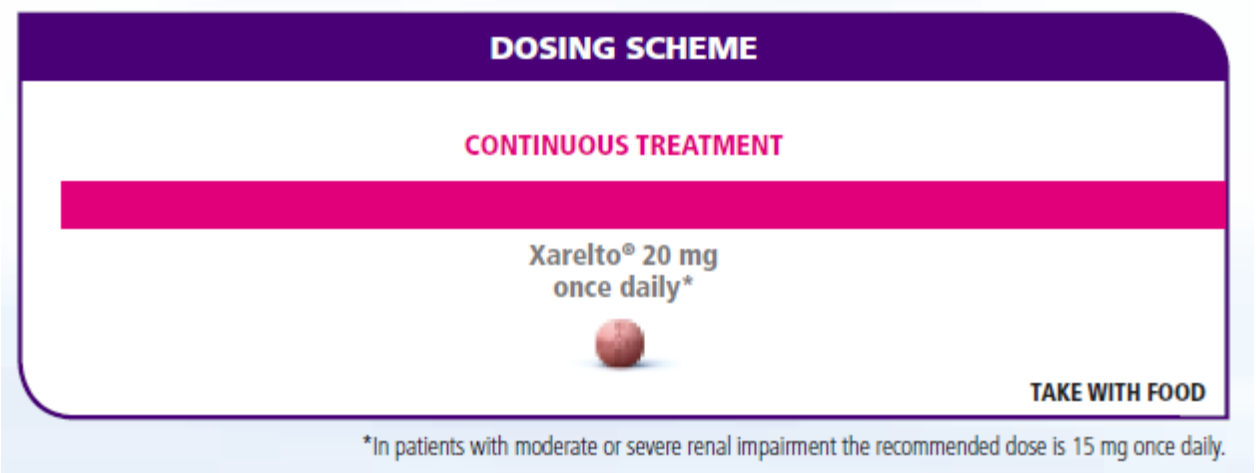
A patient alert card must be provided to each patient who is prescribed Xarelto®2.5, 15 or 20 mg, and the implications of anticoagulant treatment should be explained. Specifically, the need for compliance and signs of bleeding and when to seek medical attention should be discussed with the patient.

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.



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. Use is notrecommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

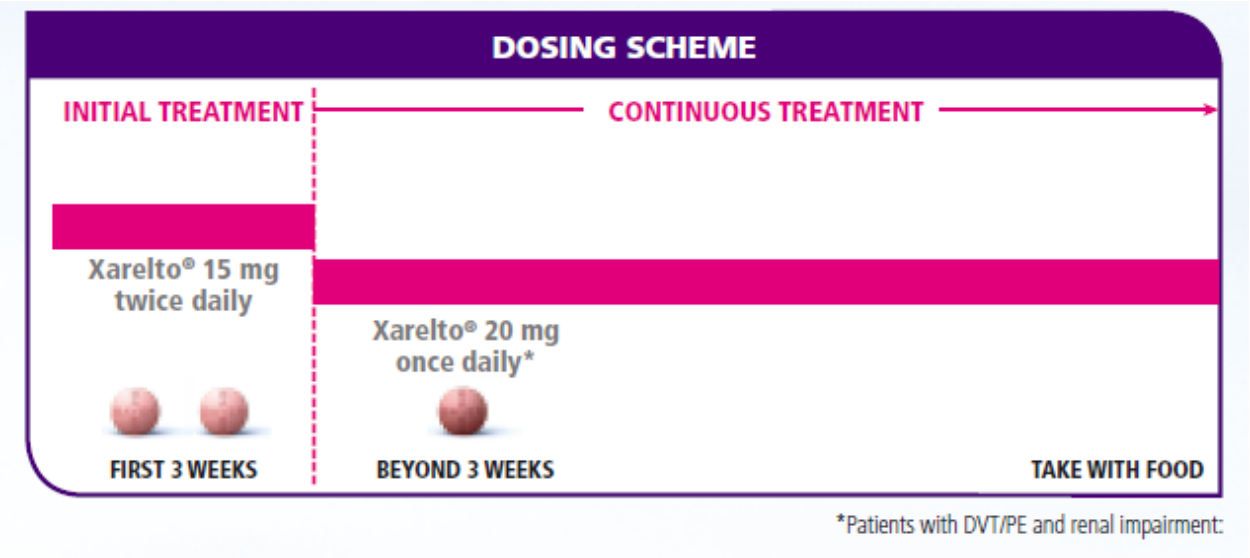
Xarelto® should be continued long term provided the benefit of stroke preventiontherapy outweighs the potential risk of bleeding.

Missed dose:

If a dose is missed the patient should take Xarelto® immediately and continue onthe following day with the once daily intake as recommended. The dose shouldnot be doubled within the same day to make up for a missed dose.

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

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



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 recurrentDVT 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 beconsidered if the patient's assessed risk for bleeding outweighs the risk forrecurrent DVT and PE. The recommendation for the use of 15 mg is based on PKmodelling and has not been studied in this clinical setting. The use of Xarelto® isnot recommended in patients with creatinine clearance < 15 ml/min.

Duration of therapy:

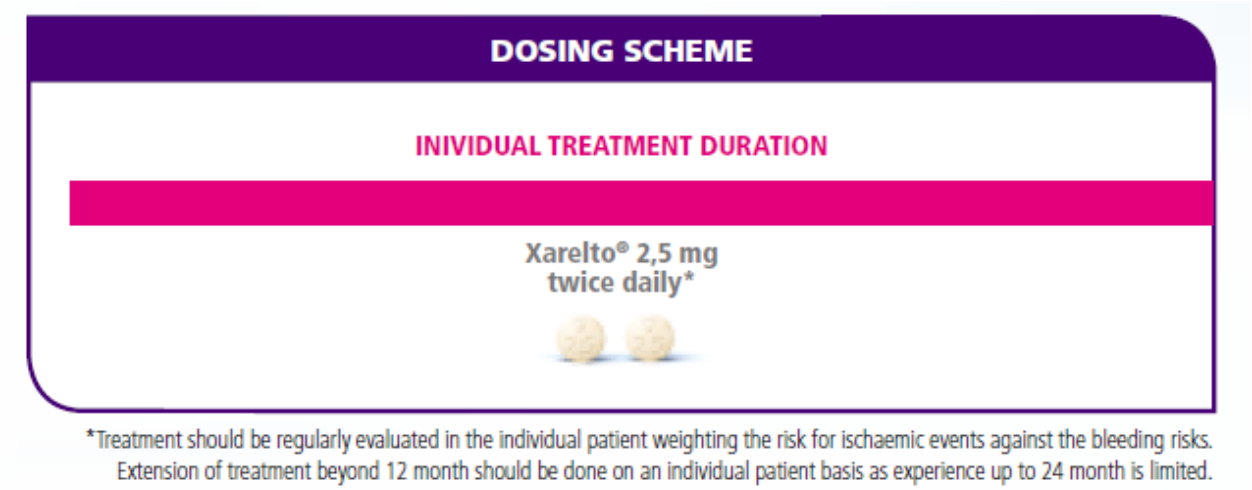
The duration of therapy should be individualized after assessment of the treatmentbenefit against the risk for bleeding.

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. 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 acutecoronary syndrome (ACS) with elevated cardiac biomarkers



The recommended dose of Xarelto® is 2.5 mg twice daily, starting as soon aspossible after stabilization of the index ACS event but earliest 24 hours afterhospital admission and at the time when parenteral anticoagulation therapy wouldnormally 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 ASA in addition to either a daily dose of 75 mgclopidogrel or a standard daily dose of ticlopidine.

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 inpatients with severe renal impairment (creatinine clearance 15 - 29 ml/min) and isnot recommended in patients with creatinine clearance <15 ml/min.

Duration of therapy:

Treatment should be regularly evaluated in the individual patient weighing therisk for ischaemic events against the bleeding risks. Extension of treatment beyond12 months should be done on an individual patient basis as experience up to 24months is limited.

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 bedoubled to make up for a missed dose.

Oral Intake

Xarelto® 2.5 mg can be taken with or without food.Xarelto® 15 mg and 20 mg must be taken with food. The intake of these doseswith food at the same time supports the required absorption of the drug, thusensuring a high oral bioavailability.

Note: Xarelto® is also available at a 10 mg dose for the prevention of venousthromboembolism (VTE) in adult patients undergoing elective hip or kneereplacement surgery. This dose can be taken with or without food similar to the2.5 mg dose.

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 Xarelto15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding

Perioperative Management

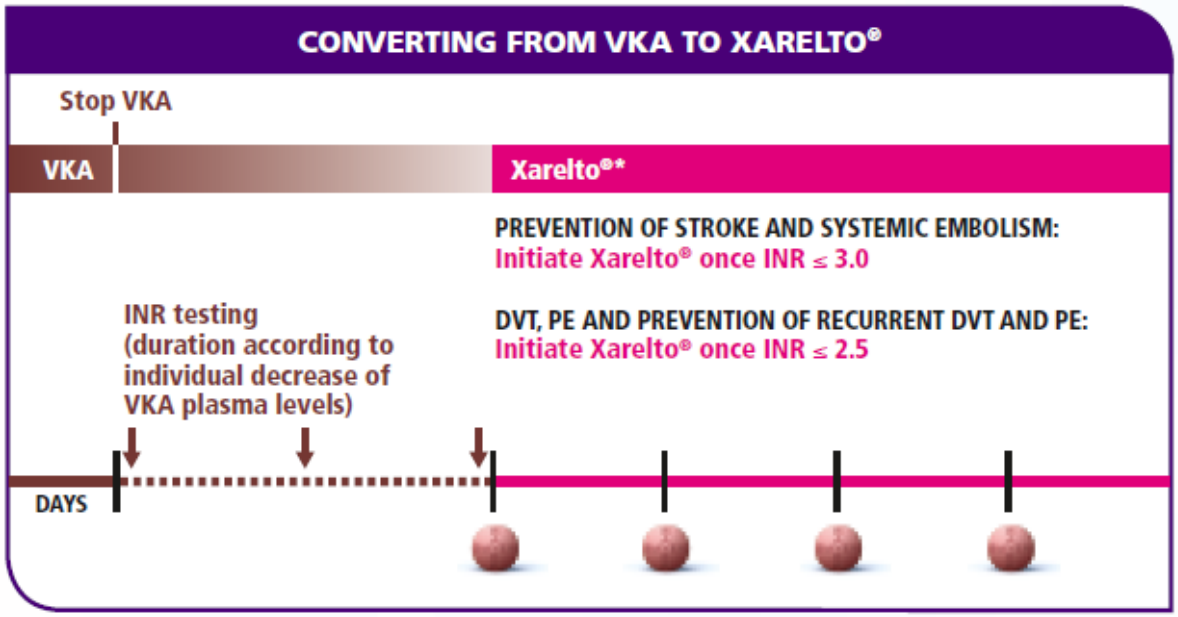
If an invasive procedure or surgical intervention is required,

- Xarelto® 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 interventionas soon as possible provided the clinical situation allows and adequate hemostasishas been established.

Converting from VKA to Xarelto®

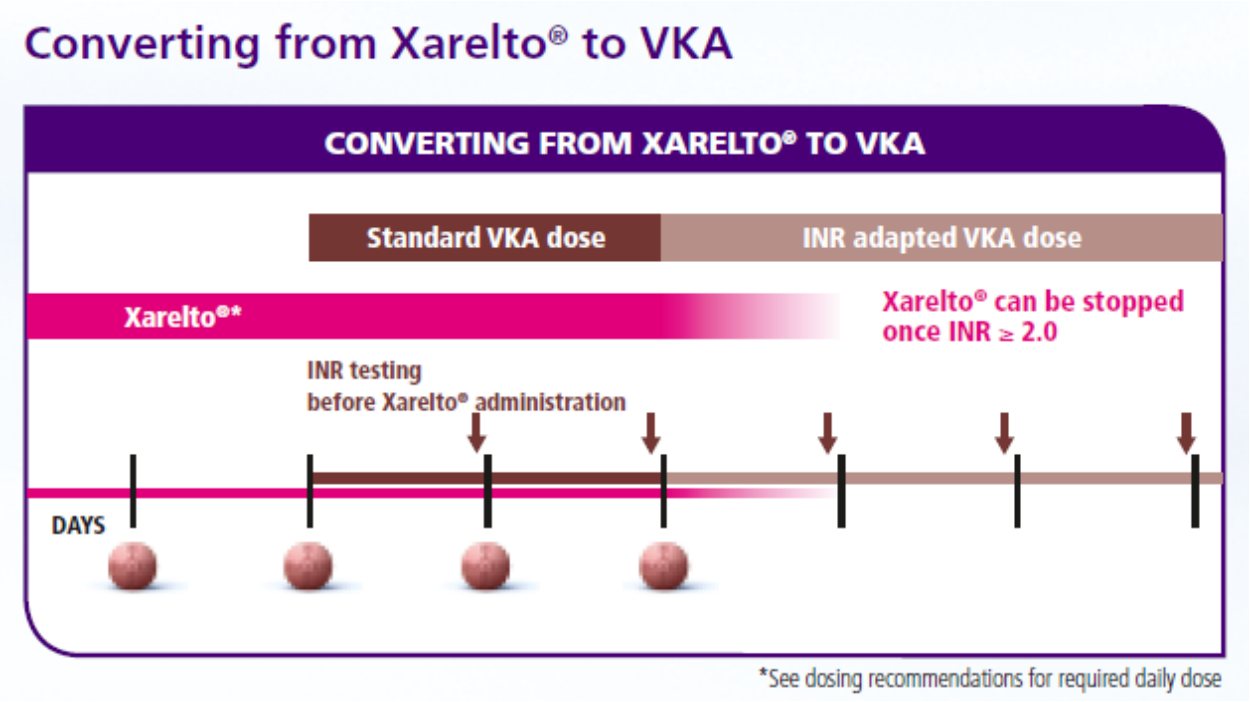


For patients treated for **prevention of stroke and systemic embolism**,treatment with VKA should be stopped and Xarelto® therapy should be initiatedwhen the **INR ≤3.0**.

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

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

Converting from Xarelto® to VKA



It is important to ensure adequate anticoagulation while minimizing the risk ofbleeding 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 dosingof VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activityof Xarelto®. While patients are on both Xarelto® and VKA the **INR should notbe tested earlier than 24 hours after the previous dose but prior to thenext dose of Xarelto®.** Once Xarelto® is discontinued, INR values obtained atleast 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: Xarelto® should be started at the time of discontinuation.

- Patients with parenteral drug on a fixed dosing scheme such as LMWH: Xarelto® should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral drug.

Converting from Xarelto® to Parenteral Anticoagulants

The first dose of the parenteral anticoagulant should be given instead of the nextXarelto® dose at the same time.

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, heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, dabigatran etexilate, apixaban etc) except under the circumstances of switching therapy to or from Xarelto® or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- with ACS who had a prior stroke or a transient ischaemic attack
- 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 carefullymonitored for signs and symptoms of bleeding complications.

Treatment decision in these patients should be done after assessment of treatmentbenefit against the risk for bleeding.

- **Patients with renal impairment:** See “dosing recommendations” forpatients with moderate (creatinine clearance 30 - 49 ml/min) or severe(15 - 29 ml/min) renal impairment. Use of Xarelto® use is not recommendedin 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
  - Drugs affecting hemostasis such as NSAIDs, acetylsalicylic acid, platelet aggregation inhibitors
  - 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 haemorragic 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

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

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

Overdose

Due to limited absorption a ceiling effect with no further increase in averageplasma exposure is expected at supratherapeutic doses of 50 mg Xarelto® andabove. The use of activated charcoal to reduce absorption in case of overdosemay be considered.

Should a bleeding complication arise in a patient receiving Xarelto®,the next Xarelto® administration should be delayed or treatment should bediscontinued 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 dialyzable.

Coagulation Testing

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

Anti-FXa assays with Xarelto®-(rivaroxaban) specific calibrators to measurerivaroxaban levels are now commercially available. If clinically indicatedhemostatic status can also be assessed by PT using Neoplastin as describedin the SmPC.

The following coagulation tests are increased: Prothrombin time (PT), activatedpartial thromboplastin time (aPTT) and calculated PT international normalizedratio (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 exceptwhen converting from Xarelto® to VKA as described above.

▼ This medicinal product is subject to additional monitoring

Xarelto® 2.5, 10, 15 and 20 mg film-coated tablets (rivaroxaban) Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: 2.5mg/10mg/15mg/20mg rivaroxaban tablet. **Indication(s):** *2.5mg* - Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers. *10mg* - Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery. *15mg/20mg* - 1. 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). 2. Treatment of deep vein thrombosis (DVT) & pulmonary embolism (PE), & prevention of recurrent DVT & PE in adults (see W&P for haemodynamically unstable PE patients). **Posology & method of administration:** *2.5mg* - Dosage 2.5 mg rivaroxaban orally twice daily; 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. Start Xarelto as soon as possible after stabilisation, including revascularisation for ACS; at the earliest 24 hours after admission & at discontinuation of parenteral anticoagulation. If dose is missed take next dose, do not double the dose. *10mg* - Dosage 10 mg rivaroxaban orally once daily; initial dose should be taken 6 to 10 hours after surgery provided haemostasis established. *Recommended treatment duration:* Dependent on individual risk of patient for VTE determined by type of orthopaedic surgery: for major hip surgery 5 weeks; for major knee surgery 2 weeks. *15mg/20mg* - *SPAF:* 20 mg orally *o.d.* with food. *DVT & PE:* 15 mg *b.i.d.* for 3 weeks followed by 20 mg *o.d.* for continued treatment & prevention of recurrent DVT & PE; take with food. *All strengths* - Refer to SmPC for full information on duration of therapy & converting to/from Vitamin K antagonists (VKA) or parenteral anticoagulants. For patients who are unable to swallow whole tablets, refer to SmPC for alternative methods of oral administration. ***Renal impairment:*** mild (creatinine clearance 50-80 ml/min) - no dose adjustment; *2.5mg /10mg* - moderate (creatinine clearance 30-49 ml/min) – no dose adjustment. Severe (creatinine clearance 15-29ml/min) - limited data indicate rivaroxaban concentrations are significantly increased, use with caution. *15mg/20mg* - moderate & severe renal impairment - limited data indicate rivaroxaban 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 patients. ***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 when switching therapy to or from rivaroxaban 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. *2.5mg* - concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or transient ischaemic attack; **Warnings & precautions:** *2.5mg* Treatment in combination with antiplatelet agents other than ASA & clopidogrel/ticlopidine has not been studied & is not recommended. Clinical surveillance in line with anticoagulation practice is recommended throughout treatment. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy – haemoglobin/haematocrit testing may be of value to detect occult bleeding. Use is not recommended in patients: with creatinine clearance <15 ml/min; receiving concomitant systemic treatment with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with increased bleeding risk (refer to SmPC); concomitantly treated with dronedarone. Use with caution in patients: with conditions with increased risk of haemorrhage (refer to SmPC); with severe renal impairment; with moderate renal impairment concomitantly receiving other medicines which increase rivaroxaban plasma concentrations;

treated concomitantly with medicines affecting haemostasis; in ACS patients > 75 years of age or with low body weight (<60kg). Patients on treatment with Xarelto & ASA or Xarelto & ASA plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk. In patients at risk of ulcerative gastrointestinal disease prophylactic treatment may be considered. Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations. *10mg* - Not recommended in patients: undergoing hip fracture surgery; receiving concomitant systemic treatment with strong CYP3A4 and P-gp inhibitors, i.e. azole-antimycotics or HIV protease inhibitors; with creatinine clearance <15 ml/min. Please note - Increased risk of bleeding therefore careful monitoring for signs/symptoms of bleeding complications & anaemia required after treatment initiation in patients: with severe renal impairment; with moderate renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations; treated concomitantly with medicinal products affecting haemostasis; with congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease (consider appropriate prophylactic treatment for at risk patients), vascular retinopathy, bronchiectasis or history of pulmonary bleeding. Take special care when neuraxial anaesthesia or spinal/epidural puncture is employed due to risk of epidural or spinal haematoma with potential neurologic complications. *15mg/20mg* - Clinical surveillance in line with anticoagulant practice is recommended throughout the treatment period. Discontinue if severe haemorrhage occurs. In studies mucosal bleedings & anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment – haemoglobin/haematocrit testing may be of value to detect occult bleeding. The following sub-groups of patients are at increased risk of bleeding & should be carefully monitored after treatment initiation so use with caution: in patients with severe renal impairment or with renal impairment concomitantly receiving medicinal products which increase rivaroxaban plasma concentrations; in patients treated concomitantly with medicines affecting haemostasis. Use is not recommended in patients: with creatinine clearance <15 ml/min; with an increased bleeding risk (refer to SmPC); receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors; with prosthetic heart valves; with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy. 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. See SmPC for full details. *10mg/15mg/20mg* - 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. *All strengths* - *Elderly population* – Increasing age may increase haemorrhagic risk. 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, ASA or platelet aggregation inhibitors due to the increased bleeding risk. Concomitant use of strong CYP3A4 inducers should be avoided unless patient is closely observed for signs and symptoms of thrombosis. **Pregnancy & breast feeding:** Contra-indicated. **Effects on ability to drive and 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, renal impairment, fever, peripheral oedema, decreased general strength & energy, increase in transaminases, post-procedural haemorrhage, contusion, wound secretion. *Serious: cf. CI/Warnings and Precautions – in addition:* thrombocythemia, angioedema and 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, abnormal hepatic function, 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 **Date of preparation:** January 2014.

Xarelto® is a trademark of the Bayer Group.

Marketing Authorisation Holder: Bayer Pharma AG, D-13342 Berlin, Germany

Further information available from: Alfred Gera and Sons Ltd. Tel: 21 446205

Version: EU/1/2014 MT

▼ 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.

Any suspected adverse drug reactions can be reported to:

Medicines Authority

Post-licensing Directorate,

203, Level 3,

Rue D'Argens,

Gżira GŻR 1368, MALTA,

or at:

http://www.medicinesauthority.gov.mt/adrportal

Telephone Number: +356 2343 9000

Or

Alfred Gera & Sons Ltd,

Triq il-Masġar,

Qormi QRM 3217,

MALTA,

or at

pv@alfredgera.com Tel: +356 21446205

EU.MT.GM XAR.12.2013.007