# Xarelto® (rivaroxaban) Prescriber Guide

November 2018

# Contents

# Patient Alert Card

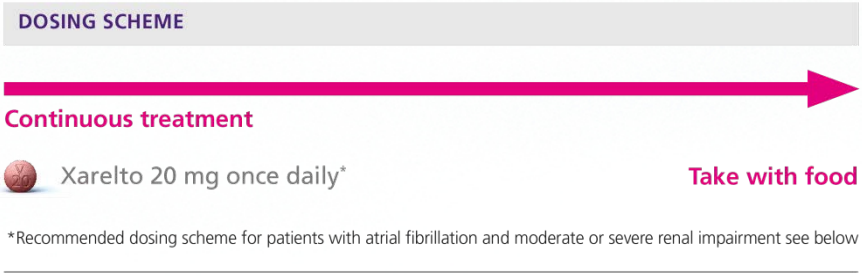
A patient alert card must be provided to each patient who is prescribed Xarelto® 2.5 mg, 10 mg, 15 mg or 20 mg and is provided with the product package. The implications of anticoagulant treatment should be explained. Specifically, the need for compliance, signs of bleeding and when to seek medical attention 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 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. ‘Xarelto’ is to be used with caution in patients with severe renal impairment (CrCl 15–29 ml/min) and is not recommended in patients with CrCl <15 ml/min.

‘Xarelto’ should be used with caution in patients with moderate renal impairment (CrCl 30-49 ml/min) concomitantly receiving other medicinal products that 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 $P2Y_{12}$ 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.

## 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 Xarelto® 15 mg **twice daily** for the first 3 weeks. This initial treatment is followed by 'Xarelto' 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 co-morbidities, 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.

## 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 Xarelto® 15 mg twice daily for the first 3 weeks.

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

'Xarelto' should be used with caution in patients with moderate renal impairment (CrCl 30-49 ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations.

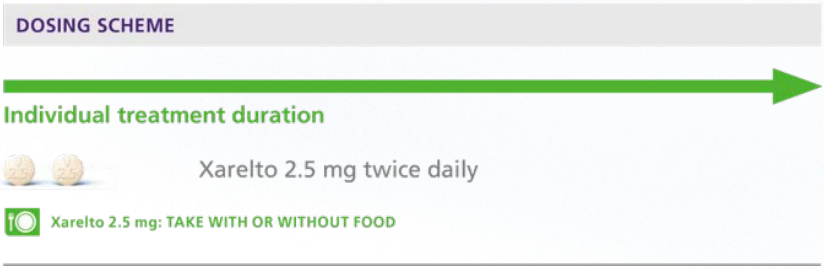
## Duration of therapy

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 '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 3 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 with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events




**Patients taking 'Xarelto' 2.5 mg twice daily should also take a daily dose of 75-100 mg acetylsalicylic acid (ASA).**

Dual antiplatelet therapy has not been studied in combination with 'Xarelto' 2.5 mg twice daily in patients with CAD and/or PAD.

### Patients with renal impairment

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

In patients with moderate renal impairment (CrCl 30–49 ml/min) concomitantly receiving other medicinal products that increase rivaroxaban plasma concentrations, 'Xarelto' 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.

### Other warnings and precautions in CAD/PAD patients

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

Concomitant treatment of CAD/PAD with 'Xarelto' 2.5 mg twice daily and ASA is contraindicated in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month

‘Xarelto’ 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 (<60 kg)

## ‘Xarelto’ 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 10 mg 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 judgement 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 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.

## For indication-specific recommendations, please refer to the sections below:

- 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 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 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 (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.

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

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

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

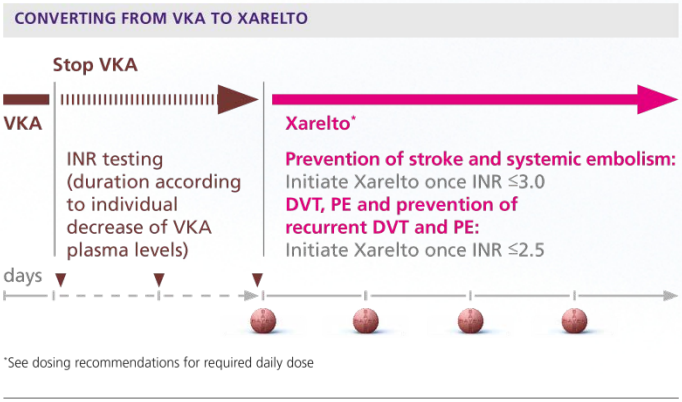
At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered. If traumatic puncture occurs the administration of rivaroxaban is to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

- 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 with ASA alone 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. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer’s prescribing information.

# Converting from VKA to Xarelto®



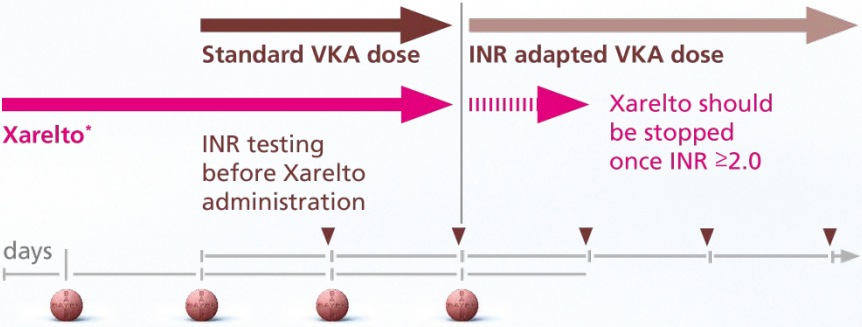

For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and Xarelto therapy should be initiated when the **INR ≤3.0**.

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

**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 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 '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 a parenteral drug on a fixed dosing scheme such as low-molecular-weight heparin (LMWH): Discontinue parenteral drug and start 'Xarelto' 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 'Xarelto' at the time of discontinuation

# 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), 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 Child-Pugh class B and C cirrhotic patients.

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. Xarelto® is to be used with caution in patients with CrCl 15–29 ml/min and in patients with moderate renal impairment (CrCl 30-49 ml/min) concomitantly receiving other medicinal products, which increase rivaroxaban plasma concentrations. Use of 'Xarelto' 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 Xarelto is not recommended
- Care is to be taken in patients concomitantly receiving drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), ASA, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs)
- CAD/PAD patients: Patients on treatment with 'Xarelto' and ASA should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk

## Patients with other haemorrhagic 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 breastfeeding. 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. Individualised 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 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’ specific calibrators to measure rivaroxaban levels are now 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 ‘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.**

# Abbreviated Prescribing Information

## Abbreviated Prescribing Information: Xarelto® 15 and 20 mg film-coated tablets Rivaroxaban

**Composition**: **The active substance** is rivaroxaban. Each tablet contains 15 mg or 20 mg of rivaroxaban. **The other ingredients** are: Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate. Tablet film coat: macrogol 3350, hypromellose, titanium dioxide (E 171), iron oxide red (E 172). **Indications**: Xarelto contains the active substance rivaroxaban and is used in adults to: • prevent blood clots in brain (stroke) and other blood vessels in patients' body if patients have a form of irregular heart rhythm called non-valvular atrial fibrillation. • treat blood clots in the veins of patients' legs (deep vein thrombosis) and in the blood vessels of patients' lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of patients' legs and/or lungs. Xarelto belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots. **How much to prescribe** --To prevent blood clots in brain (stroke) and other blood vessels in the body. The recommended dose is one tablet Xarelto 20 mg once a day. If patients have kidney problems, the dose may be reduced to one tablet Xarelto 15 mg once a day. If patients need a procedure to treat blocked blood vessels in their heart (called a percutaneous coronary intervention – PCI with an insertion of a stent), there is limited evidence to reduce the dose to one tablet Xarelto 15 mg once a day (or to one tablet Xarelto 10 mg once a day in case patients' kidneys are not working properly) in addition to an antiplatelet medicinal product such as clopidogrel. --To treat blood clots in the veins of the legs and blood clots in the blood vessels of the lungs, and for preventing blood clots from re-occurring: The recommended dose is one tablet Xarelto 15 mg twice a day for the first 3 weeks. For treatment after 3 weeks, the recommended dose is one tablet Xarelto 20 mg once a day. After at least 6 months blood clot treatment the doctor may decide to continue treatment with either one 10 mg tablet once a day or one 20 mg tablet once a day. If patients have kidney problems and take one tablet Xarelto 20mg once a day, the doctor may decide to reduce the dose for the treatment after 3 weeks to one tablet Xarelto 15 mg once a day if the risk for bleeding is greater than the risk for having another blood clot. Patients should swallow the tablet(s) preferably with water. Prescribe Xarelto together with a meal. The tablet may be crushed and mixed with water or apple puree immediately before patients take it. This mixture should be immediately followed by food. If necessary, the doctor may also give patients the crushed Xarelto tablet through a stomach tube. **Contraindications**: if patients are allergic to rivaroxaban or any of the other ingredients of this medicine • if patients are bleeding excessively • if patients have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g. stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes) • if patients are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open• if patients have a liver disease which leads to an increased risk of bleeding • if patients are pregnant or breast feeding. **Warnings and Precautions:** -- if patients have an increased risk of bleeding, as could be the case in situations such as: • severe kidney disease, since patients' kidney function may affect the amount of medicine that works in patients' body• if patients are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open • bleeding disorders• very high blood pressure, not controlled by medical treatment• diseases of patients' stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) • a problem with the blood vessels in the back of patients' eyes (retinopathy) • a lung disease where patients' bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from patients' lung --if patients have a prosthetic heart valve --if patients determines that patients' blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from patients' lungs is planned. **If patients need to have an operation:** -- it is very important to take Xarelto before and after the

operation exactly at the times patients have been told by their doctor. -- If patients' operation involves a catheter or injection into patients' spinal column (e.g. for epidural or spinal anaesthesia or pain reduction): • it is very important to take Xarelto before and after the injection or removal of the catheter exactly at the times patients have been told by their doctor • patients should tell their doctors immediately if they get numbness or weakness of their legs or problems with their bowel or bladder after the end of anaesthesia, because urgent care is necessary. **Children and adolescents** Xarelto **is not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents. **Drug-drug interactions**: • some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin • some anti-viral medicines for HIV / AIDS (e.g. ritonavir) • other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol) • anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid) • dronedarone, a medicine to treat abnormal heart beat • some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)) the effect of Xarelto may be increased with the previously mentioned drugs.• some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital) • St John's Wort (Hypericum perforatum), a herbal product used for depression• rifampicin, an antibiotic. the effect of Xarelto may be reduced with these drugs. **Pregnancy and breast feeding** Do not prescribe Xarelto if patients are pregnant or breast feeding. If there is a chance that patients could become pregnant, prescribe a reliable contraceptive while patients are taking Xarelto. **Driving and using machines** Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect). Patients should not drive or use machines if they are affected by these symptoms. **Xarelto contains lactose. Side effects**: **Common (may affect up to 1 in 10 people):** • bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum • bleeding into the eye (including bleeding from the whites of the eyes) • bleeding into tissue or a cavity of the body (haematoma, bruising) • coughing up blood• bleeding from the skin or under the skin • bleeding following an operation • oozing of blood or fluid from surgical wound • swelling in the limbs • pain in the limbs • fever • reduction in red blood cells which can make the skin pale and cause weakness or breathlessness • stomach ache, indigestion, feeling or being sick, constipation, diarrhea • low blood pressure (symptoms may be feeling dizzy or fainting when standing up) • decreased general strength and energy (weakness, tiredness), headache, dizziness • rash, itchy skin • impaired function of the kidneys • blood tests may show an increase in some liver enzymes. **Uncommon** (may affect up to 1 in 100 people): • bleeding into the brain or inside the skull • bleeding into a joint causing pain and swelling • fainting • feeling unwell • dry mouth • faster heartbeat • allergic reactions, including allergic skin reactions • hives • impaired function of the liver • blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets. **The following side effects have been reported since authorisation**: • Angioedema and allergic oedema (swelling of the face, lips, mouth, tongue or throat). • Cholestasis (decreased bile flow), Hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury) • Thrombocytopenia (low number of platelets, which are cells that help blood to clot). **Reporting of side effects** If patients get any side effects, they should talk to their doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, patients can help provide more information on the safety of this medicine. **To report any side effect(s):** National Pharmacovigilance and Drug Safety Center (NPC). Fax: + 966 - 11 - 205 - 7662. Call NPC at +966 - 11 - 2038222, Ext.: 2317 - 2356 - 2353 - 2354 - 2334 - 2340. Toll - free: 8002490000. E - mail: npc.drug@sfda.gov.sa. Website: www.sfda.gov.sa/npc **Manufacturer** Bayer Pharma AG 51368 Leverkusen, Germany **Marketing Authorisation Holder** Bayer AG Kaiser-Wilhelm-Allee 1 51373 Leverkusen, Germany. **This leaflet was last revised in October, 2017.**

## Abbreviated Prescribing Information: Xarelto 10mg - Film coated tablet Rivaroxaban

**Composition**: • **The active substance** is rivaroxaban. Each tablet contains 10 mg of rivaroxaban. • **The other ingredients** are: Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate. Tablet film coat: macrogol 3350, hypromellose, titanium dioxide (E 171), iron oxide red (E 172). **Indications**: Xarelto contains the active substance rivaroxaban and is prescribed in adults to: • prevent blood clots in the veins after a hip or knee replacement operation. Patients' doctor has prescribed this medicine for them because after an operation they are at an increased risk of getting blood clots. • treat blood clots in the veins of patients' legs (deep vein thrombosis) and in the blood vessels of patients' lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of patient's legs and/or lungs. Xarelto belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots. **How much to prescribe** • To prevent blood clots in the veins after a hip or knee replacement operation The recommended dose is one tablet Xarelto 10 mg once a day. • To treat blood clots in the veins of the legs and blood clots in the blood vessels of the lungs, and for preventing blood clots from re-occurring After at least 6 months blood clot treatment, the recommended dose is either one 10 mg tablet once a day or one 20 mg tablet once a day. Patients should swallow the tablet preferably with water. Xarelto can be prescribed with or without food. If patients have difficulty swallowing the tablet whole, the tablet may be crushed and mixed with water or apple puree immediately before patients take it. If necessary, the doctor may also give patients the crushed Xarelto tablet through a stomach tube. **To prevent blood clots in the veins after a hip or knee replacement operation:** Prescribe the first tablet 6 - 10 hours after the operation. If patients have had a major hip operation they should usually take the tablets for 5 weeks. If patients have had a major knee operation they should usually take the tablets for 2 weeks. **Contraindications**: • if patients are allergic to rivaroxaban or any of the other ingredients of this medicine • if patients are bleeding excessively • if patients have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g. stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes) • if patients are taking medicines to prevent blood clotting (e.g. warfarin dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open • if patients have a liver disease which leads to an increased risk of bleeding • if patients are pregnant or breast feeding. • if patients have an increased risk of bleeding, as could be the case in situations such as: --moderate or severe kidney disease, since patients' kidney function may affect the amount of medicine that works in patients' body --if patients are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open --bleeding disorders --very high blood pressure, not controlled by medical treatment --diseases of patients' stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) --a problem with the blood vessels in the back of patients' eyes (retinopathy) --a lung disease where patients' bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from patients' lung --if patients have a prosthetic heart valve --if patients' doctor determines that patients' blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from patients' lungs is planned. **Warnings and Precautions:** If patients need to have an operation: • it is very important to prescribe Xarelto before and after the operation exactly at the times patients have been told by patients' doctor. • If patients' operation involves a catheter or injection into patients' spinal column (e.g. for epidural or spinal anaesthesia or pain reduction): --it is very important to

prescribe Xarelto exactly at the times patients have been told by patients' doctor --tell patients' doctor immediately if patients get numbness or weakness of their legs or problems with their bowel or bladder after the end of anaesthesia, because urgent care is necessary. Children and adolescents Xarelto is not recommended for people under 18 years of age. There is not enough information on its use in children and adolescents. **Drug-drug interactions**: --some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin --some anti-viral medicines for HIV / AIDS (e.g. ritonavir) --other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol) --anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid) --dronedarone, a medicine to treat abnormal heart beat --some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)). These medicines may increase the effect of Xarelto. --some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital) --St John's Wort (Hypericum perforatum), a herbal product used for depression. --rifampicin, an antibiotic. These medicines may reduce the effect of Xarelto. **Pregnancy and breast feeding** Do not prescribe Xarelto if patients are pregnant or breast feeding. If there is a chance that patients could become pregnant, prescribe a reliable contraceptive while patients are taking Xarelto. **Driving and using machines** Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect). Patients should not drive or use machines if they are affected by these symptoms. **Xarelto contains lactose. Side effects**: **Common** (may affect up to 1 in 10 people): • bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum • bleeding into the eye (including bleeding from the whites of the eyes) • bleeding into tissue or a cavity of the body (haematoma, bruising) • coughing up blood • bleeding from the skin or under the skin • bleeding following an operation • oozing of blood or fluid from surgical wound • swelling in the limbs • pain in the limbs • fever • reduction in red blood cells which can make the skin pale and cause weakness or breathlessness • stomach ache, indigestion, feeling or being sick, constipation, diarrhea • low blood pressure (symptoms may be feeling dizzy or fainting when standing up) • decreased general strength and energy (weakness, tiredness), headache, dizziness • rash, itchy skin • impaired function of the kidneys (may be seen in tests performed by patients' doctor) • blood tests may show an increase in some liver enzymes. **Uncommon** (may affect up to 1 in 100 people): • bleeding into the brain or inside the skull • bleeding into a joint causing pain and swelling • fainting • feeling unwell • dry mouth • faster heartbeat • allergic reactions, including allergic skin reactions • hives • impaired function of the liver (may be seen in tests performed by patients' doctor) • blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets. **The following side effects have been reported since authorisation**: • Angioedema and allergic oedema (swelling of the face, lips, mouth, tongue or throat). • Cholestasis (decreased bile flow), Hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury) • Thrombocytopenia (low number of platelets, which are cells that help blood to clot). **Reporting of side effects** If patients get any side effects, they should talk to their doctor or pharmacist. This includes any possible side effects not listed in insert leaflet. By reporting side effects, patients can help provide more information on the safety of this medicine. **To report any side effect(s):** National Pharmacovigilance and Drug Safety Center (NPC). Fax: + 966 - 11 - 205 - 7662. Call NPC at +966 - 11 - 2038222, Ext.: 2317 - 2356 - 2353 - 2354 - 2334 - 2340. Toll - free: 8002490000. E - mail: npc.drug@sfda.gov.sa. Website: www.sfda.gov.sa/npc **Manufacturer** Bayer Pharma AG 51368 Leverkusen Germany **Marketing Authorisation Holder** Bayer AG Kaiser-Wilhelm-Allee 1 51373 Leverkusen, Germany. **This leaflet was last revised in October, 2017.**

## Abbreviated Prescribing Information: Xarelto 2.5 mg film-coated tablets Rivaroxaban

**Composition**: **The active substance** is rivaroxaban. Each tablet contains Xarelto 2.5 mg of rivaroxaban. **The other ingredients** are: Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose, sodium laurilsulfate, magnesium stearate. Tablet film coat: macrogol 3350, hypromellose, titanium dioxide (E 171), iron oxide yellow (E 172). **Indications**: For Adult patients with high risk of getting a blood clot due to a coronary artery disease or peripheral artery disease which causes symptoms. Xarelto reduces the risk in adults of getting blot clots (atherothrombotic events). Xarelto will not be given on its own. The doctor will also prescribe acetylsalicylic acid. Xarelto contains the active substance rivaroxaban and belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots. **How much to prescribe** --The recommended dose is one 2.5 mg tablet twice a day. Take Xarelto around the same time every day (for example, one tablet in the morning and one in the evening). The tablet may be crushed and mixed with water or apple puree immediately before taking it. If necessary, the doctor may also give the crushed Xarelto tablet through a stomach tube. Xarelto will not be given on its own. The doctor will also prescribe acetylsalicylic acid. The doctor will decide how much of these to take (usually between 75 to 100 mg acetylsalicylic acid daily). **When to start Xarelto—**The doctor will decide when to start treatment with Xarelto if the patient has been diagnosed with coronary artery disease or peripheral artery disease. The doctor will decide how long the patient must continue treatment. **Contraindications**: if the patient is allergic to rivaroxaban or any of the other ingredients of this medicine • if the patient is bleeding excessively • if the patient has a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes) • if the patient is taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open • if the patient has an acute coronary syndrome and previously had a bleeding or a blood clot in the brain 2.5 mg rivaroxaban (stroke) • if the patient has a liver disease which leads to an increased risk of bleeding • if the patient is pregnant or breast feeding. **Warnings and Precautions:** -- Xarelto should not be used in combination with certain other medicines which reduce blood clotting such as prasugrel or ticagrelor other than aspirin and clopidogrel/ticlopidine. **Special care should be taken with Xarelto** if the patient has an increased risk of bleeding, as could be the case in situations such as: --severe kidney disease, since the kidney function may affect the amount of medicine that works in the body --if the patient is taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section “Other medicines and Xarelto”) --bleeding disorders --very high blood pressure,not controlled by medical treatment --diseases of the stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) --a problem with the blood vessels in the back of the eyes (retinopathy) --a lung disease where the bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from the lung --patient older than 75 years -- weigh 60 kg or less –patient with a prosthetic heart valve **If patients need to have an operation:** -- it is very important to take Xarelto before and after the operation exactly at the times patients have been told by their doctor. -- If patients’ operation involves a catheter or injection into patients’ spinal column (e.g. for epidural or spinal anaesthesia or pain reduction): • it is very important to take Xarelto before and after

the injection or removal of the catheter exactly at the times patients have been told by their doctor • Pateint should tell the doctor immediately if they get numbness or weakness of their legs or problems with their bowel or bladder after the end of anaesthesia, because urgent care is necessary. **Children and adolescents** Xarelto **is not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents. **Drug-drug interactions**: • some medicines for fungal infections (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin • some anti-viral medicines for HIV / AIDS (e.g. ritonavir) • other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol) • anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid) • dronedarone, a medicine to treat abnormal heart beat • some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)) the effect of Xarelto may be increased with the previously mentioned drugs.• some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital) • St John's Wort (Hypericum perforatum), a herbal product used for depression• rifampicin, an antibiotic. The effect of Xarelto may be reduced with these drugs. **Pregnancy and breast feeding** Do not prescribe Xarelto if patients are pregnant or breast feeding. If there is a chance that patients could become pregnant, precribe a reliable contraceptive while patients are taking Xarelto. **Driving and using machines** Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect). Patients should not drive or use machines if they are affected by these symptoms. **Xarelto contains lactose and Sodium** This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free". **Side effects**: **Common (may affect up to 1 in 10 people):** • bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum • bleeding into the eye (including bleeding from the whites of the eyes) • bleeding into tissue or a cavity of the body (haematoma, bruising) • coughing up blood• bleeding from the skin or under the skin • bleeding following an operation • oozing of blood or fluid from surgical wound • swelling in the limbs • pain in the limbs • fever • reduction in red blood cells which can make the skin pale and cause weakness or breathlessness • stomach ache, indigestion, feeling or being sick, constipation, diarrhea • low blood pressure (symptoms may be feeling dizzy or fainting when standing up) • decreased general strength and energy (weakness, tiredness), headache, dizziness • rash, itchy skin • impaired function of the kidneys • blood tests may show an increase in some liver enzymes. **Uncommon** (may affect up to 1 in 100 people): bleeding into the brain or inside the skull • bleeding into a joint causing pain and swelling • fainting • feeling unwell • dry mouth • faster heartbeat • allergic reactions, including allergic skin reactions • Thrombocytopenia (low number of platelets, which are cells that help blood to clot) • hives • impaired function of the liver (may be seen in tests performed by the doctor) • blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets. **Reporting of side effects** If patients get any side effects, they should talk to their doctor or pharmacist. This includes any possible side effects not listed in this leaflet. By reporting side effects, patients can help provide more information on the safety of this medicine. To report any side effect(s): National Pharmacovigilance and Drug Safety Center (NPC) Fax: + 966 – 11 – 205 – 7662 To Contact the executive management of the vigilance and crisis management Telephone: + 966 – 11 – 2038222 Extension: 2353 – 2356 – 2317 – 2354 – 2334 – 2340 Toll free: 8002490000 Email : npc.drug@sfda.gov.sa Website: www.sfda.gov.sa/npc. **Manufacturer and Marketing Authorization Holder** Bayer Pharma AG 51368 Leverkusen, Germany. **This leaflet was last revised in August, 2018.**

# Dosing Overview

| INDICATION[1] | DOSING[1] | SPECIAL POPULATIONS[1] |
|---|---|---|
| **Stroke prevention** in adult patients with non-valvular atrial fibrillation[a] | **Xarelto® 20 mg once daily** | In patients with impaired renal function with CrCl 15–49 ml/min[b]<br>**'Xarelto' 15 mg once daily**<br><br>PCI with stent placement<br>For a maximum of 12 months<br>**'Xarelto' 15 mg once daily**<br>plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel)<br><br>PCI with stent placement<br>In patients with impaired renal function with creatinine clearance 30–49 ml/min[b]<br>**'Xarelto' 10 mg once daily**<br>plus a $P2Y_{12}$ inhibitor (e.g. clopidogrel) |
| Treatment of **DVT** and **PE**[c], and prevention of recurrent DVT and PE in adult patients | Treatment and prevention of recurrence, day 1–21<br>**'Xarelto' 15 mg twice daily**<br><br>Prevention of recurrence, from day 22 onwards<br>**'Xarelto' 20 mg once daily**<br><br>Extended prevention of recurrence, from month 7 onwards<br>**'Xarelto' 10 mg once daily**<br><br>Extended prevention of recurrence, from month 7 onwards<br>**'Xarelto' 20 mg once daily**<br>in patients at high risk of recurrent DVT or PE, such as those:<br>♦ With complicated comorbidities<br>♦ Who have developed recurrent DVT or PE on extended prevention with 'Xarelto' 10 mg | In patients with impaired renal function with CrCl 15–49 ml/min[b]<br>Treatment and prevention of recurrence, day 1–21<br>**'Xarelto' 15 mg twice daily**<br><br>Thereafter **'Xarelto' 15 mg once daily** instead of 'Xarelto' 20 mg once daily if patient's assessed risk for bleeding outweighs risk for recurrence<br><br>When the recommended dose is 'Xarelto' 10 mg once daily, no dose adjustment is necessary |
| Prevention of VTE in adults undergoing elective **hip or knee replacement surgery** | **'Xarelto' 10 mg once daily** | |
| Prevention of atherothrombotic events in adult patients with **CAD** or **symptomatic PAD** at high risk of ischaemic events | **'Xarelto' 2.5 mg twice daily in combination with acetylsalicylic acid**<br>75–100 mg/day | |

**'Xarelto' 15 mg and 20 mg should be taken with food[1]**

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

[a]With one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack. [b]Use with caution in patients with creatinine clearance 15–29 ml/min and in patients with creatinine clearance 30–49 ml/min when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration. [c]Not recommended as an alternative to unfractionated heparin in patients with PE who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

**Reference:** 1. Xarelto (rivaroxaban). Summary of Product Characteristics, as approved by the European Commission.

# Reporting adverse drug reactions

To report any side effect(s):
Saudi Food and Drug Authority (SFDA)

SFDA call center: 19999
Toll free phone: 8002490000
Fax: +966-11-2057662
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Or

Pharmacovigilance department in Bayer Saudi LLC:
Bayer Saudi Arabia LLC.

Al Kamal Import Office
Ittihad St. P.O Box 15369
21444 Jeddah, Saudi Arabia
Tel.: +9661 2 6571675
Fax: +9661 2 6534992
Email**:** pv.me@bayer.com

# Notes

## Notes

# Notes