



Xarelto[®] (rivaroxaban) Prescriber Guide

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Prescriber Guide

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

Patient Alert Card

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

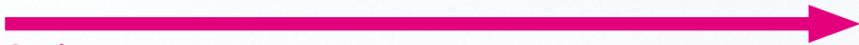
The patient alert card will inform physicians and dentists about the patient's anticoagulation treatment and will contain emergency contact information. The patient should be instructed to carry the patient alert card at all times and present it to every healthcare provider.

Dosing recommendations

Stroke prevention in adult patients with non-valvular atrial fibrillation

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

DOSING SCHEME



Continuous treatment



Xarelto 20 mg once daily*

Take with food

*Recommended dosing scheme for patients with atrial fibrillation and moderate or severe renal impairment see below

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 renal impairment 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 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.

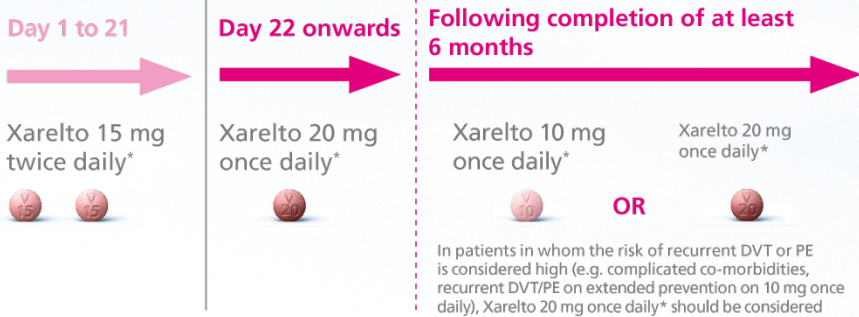
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, 'Xarelto' treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion 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.

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.

DOSING SCHEME



 Xarelto 10 mg: TAKE WITH OR WITHOUT FOOD – Xarelto 15/20 mg: MUST BE TAKEN WITH FOOD

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

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 renal impairment 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

DOSING SCHEME

Individual treatment duration 



Xarelto 2.5 mg twice daily



Xarelto 2.5 mg: TAKE WITH OR WITHOUT FOOD

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

In patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, treatment should not be started until haemostasis is achieved (see also section 5.1 of the SmPC)

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.

Co-administration with antiplatelet therapy

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

Other warnings and precautions in CAD/PAD patients

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

In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of Xarelto 2.5 mg twice daily have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided. Patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months. (see also section 5.1 of the SmPC).

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

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

'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)
- ◆ In CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with Xarelto.

'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 are to be taken with food. The intake of these doses with food at the same time supports the required absorption of the drug, thus ensuring a high oral bioavailability.

For patients who are unable to swallow whole tablets, a 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: if possible and based on the clinical judgement of the physician:

- ◆ 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.

Indication-specific recommendations:

- ◆ Prevention of stroke and systemic embolism in adult patients with NVAf /
- ◆ Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients

There is no clinical experience with the use of 15 mg and 20 mg Xarelto® in these situations. To reduce the potential risk of bleeding associated with the concurrent use of Xarelto and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xarelto. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Xarelto is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

For the removal of an epidural catheter and based on the general pharmacokinetic characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of Xarelto. Following removal of the catheter, at least 6 hours should elapse before the next Xarelto dose is administered. If traumatic puncture occurs, the administration of Xarelto 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 Xarelto and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Xarelto.

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

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

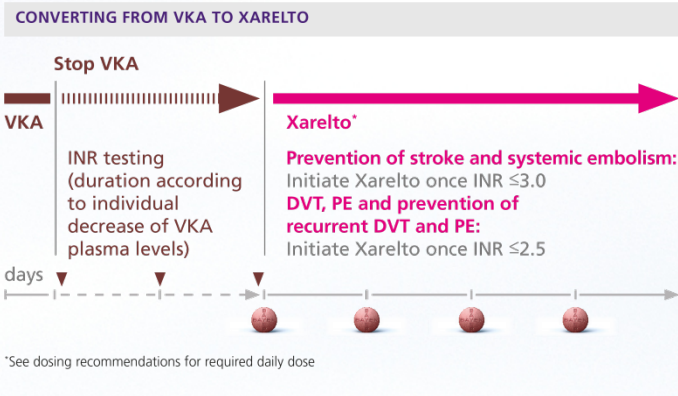
- ◆ Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

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

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

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

Converting from VKA to Xarelto



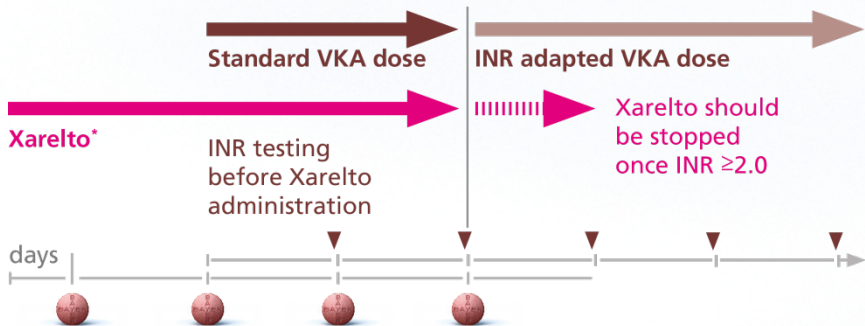
For patients treated for **prevention of stroke and systemic embolism**, treatment with VKA should be stopped and Xarelto therapy should be initiated when the **INR ≤ 3.0** .

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 concurrently until the **INR ≥ 2.0** . For the first 2 days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing.

INR measurement is not appropriate to measure the anticoagulant activity of 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.

Elderly population: The risk of bleeding increases with increasing age.

Several subgroups of patients are at increased risk and should be carefully monitored for signs and symptoms of bleeding complications.

Treatment decision in these patients should be carried out after assessment of treatment benefit against the risk for bleeding.

Patients with renal impairment

See dosing recommendations for patients with moderate (CrCl 30–49 ml/min) or severe (CrCl 15–29 ml/min) renal impairment. Xarelto is to be used with caution in patients with CrCl 15–29 ml/min and in patients with renal impairment (CrCl concomitantly receiving other medicinal products that increase rivaroxaban 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 antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk
- ◆ The interaction with erythromycin, clarithromycin or fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients (For patients with renal impairment see further above)

Patients with other haemorrhagic risk factors

As with other antithrombotics, 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

Patients with cancer

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during Xarelto therapy.

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

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. A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa). The use of activated charcoal to reduce absorption in case of overdose may be considered.

Should a bleeding complication arise in a patient receiving 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
- ◆ If bleeding cannot be controlled with the above measures, either administration of a specific factor Xa inhibitor reversal agent (andexanet alfa) or a specific procoagulant reversal agent such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa) should be considered. However, there is

currently very limited clinical experience with the use of these medicinal products in individuals receiving 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 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.

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Abbreviated Prescribing Information

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

Xarelto® 15 and 20 mg - Composition: Each film-coated tablet contains 15 mg or 20 mg of rivaroxaban. **Indications:** Xarelto® is used in adults to: Prevent blood clots in brain (stroke) and other blood vessels in your body if you have a form of irregular heart rhythm called non-valvular atrial fibrillation. To treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your 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 patients 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. **Side effects: Common (may affect up to 1 in 10 people):** • reduction in red blood cells which can make the skin pale and cause weakness or breathlessness • 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 • 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. **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): The National Pharmacovigilance Centre (NPC) - Fax: +966-11-205-7662, SFDA Call Center: 19999,

E-mail: npc.drug@sfd.gov.sa - Website: <https://ade.sfd.gov.sa>

- Please refer to package insert leaflet (PIL) for full prescribing info.

Marketing Authorisation Holder Bayer AG Kaiser-Wilhelm-Allee 1 51373 Leverkusen, Germany.

SA Revised PIL version: July 2019

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

Xarelto[®] 10 mg - Composition: Each film coated tablet contains 10 mg of rivaroxaban.

Indications: Xarelto[®] 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 esophagus)
 - 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 the doctor immediately if patients get numbness or weakness of their legs or problems with their bowel or bladder after the end of anesthesia, 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): • reduction in red blood cells which can make the skin pale and cause weakness or breathlessness • 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 • 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.

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):

The National Pharmacovigilance Centre (NPC) - Fax: +966-11-205-7662, SFDA Call Center: 19999, E-mail: npc.drug@sfda.gov.sa - Website: <https://ade.sfda.gov.sa>

- Please refer to the product Package Insert Leaflet (PIL) for full prescribing data

Marketing Authorisation Holder: Bayer AG - Bayer AG, Kaiser-Wilhelm-Allee 1 51373
Leverkusen, Germany SA PIL version: July 2019

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

Xarelto® 2.5 mg film-coated tablets - **Composition:** Each tablet contains 2.5 mg of rivaroxaban which belongs to a group of medicines called antithrombotic agents.

Indications: Xarelto® reduces the risk in adults of getting blot clots (atherothrombotic events) due to a coronary artery disease (CAD)or peripheral artery disease (PAD) which causes symptoms. **How it works:** It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots. Xarelto® will not be given on its own. The doctor will also prescribe acetylsalicylic.

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 (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 - 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 • Patient 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, 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 and Sodium** This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free". **Side effects: Common:** • 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, diarrhoea • 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.

- **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@sfd.gov.sa. Website: www.sfd.gov.sa/npc
- **Please refer to the product Package Insert Leaflet (PIL) for full details & usage information**

Marketing Authorization Holder: Bayer AG Kaiser-Wilhelm-Allee 1 - 51373 Leverkusen, Germany

SA PIL version: July. 2019

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 Xarelto 15 mg once daily PCI with stent placement For a maximum of 12 months Xarelto 15 mg once daily plus a P2Y ₁₂ inhibitor (e.g. clopidogrel) PCI with stent placement In patients with impaired renal function with creatinine clearance 30–49 ml/min ^b Xarelto 10 mg once daily 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 Xarelto 15 mg twice daily Prevention of recurrence, from day 22 onwards Xarelto 20 mg once daily Extended prevention of recurrence, from month 7 onwards Xarelto 10 mg once daily Extended prevention of recurrence, from month 7 onwards Xarelto 20 mg once daily in patients at high risk of recurrent DVT or PE, such as those: ♦ With complicated comorbidities ♦ 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 Treatment and prevention of recurrence, day 1–21 Xarelto 15 mg twice daily Thereafter Xarelto 15 mg once daily instead of Xarelto 20 mg once daily if patient's assessed risk for bleeding outweighs risk for recurrence 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 75–100 mg/day	

Xarelto® 15 mg and 20 mg should be taken with food¹

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.

^aWith one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. ^bUse with caution in patients with creatinine clearance 15–29 ml/min and in patients with renal impairment when concomitantly receiving other medicinal products that increase rivaroxaban plasma concentration. ^cNot 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 6573015
Fax: +9661 2 6534992
Email: pv.me@bayer.com
For medical information: med-info.me@bayer.com

This material has been approved by the Saudi FDA

SA – Xarelto – PG – V2.1
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