

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 2.5 mg rivaroxaban.

### Excipient with known effect

Each film-coated tablet contains 33.92 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film-coated tablet (tablet)

Light yellow, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "2.5" and a triangle on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

Xarelto, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

### **4.2 Posology and method of administration**

#### Posology

The recommended dose is 2.5 mg twice daily.

- ACS

Patients taking Xarelto 2.5 mg twice daily should also take a daily dose of 75 - 100 mg ASA or a daily dose of 75 - 100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited (see section 5.1).

Treatment with Xarelto should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

- CAD/PAD

Patients taking Xarelto 2.5 mg twice daily should also take a daily dose of 75 - 100 mg 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 section 5.1).

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.

- ACS, CAD/PAD

*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.

Safety and efficacy of Xarelto 2.5 mg twice daily in combination with dual antiplatelet therapy have been studied in patients

- with recent ACS in combination with ASA plus clopidogrel/ticlopidine (see section 4.1), and
- after recent revascularisation procedure of the lower limb due to symptomatic PAD in combination with ASA and, if applicable, short-term clopidogrel use (see sections 4.4 and 5.1)

*Missed dose*

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

*Converting from Vitamin K Antagonists (VKA) to Xarelto*

When converting patients from VKAs to Xarelto, International Normalised Ratio (INR) values could be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

*Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. 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 testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

*Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

*Converting from Xarelto to parenteral anticoagulants*

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

*Special populations*

Renal impairment

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance  $< 15$  ml/min (see sections 4.4 and 5.2).

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

#### Elderly population

No dose adjustment (see sections 4.4 and 5.2)

The risk of bleeding increases with increasing age (see section 4.4).

#### Body weight

No dose adjustment (see sections 4.4 and 5.2)

#### Gender

No dose adjustment (see section 5.2)

#### Paediatric population

The safety and efficacy of Xarelto 2.5 mg tablets in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto 2.5 mg tablets are not recommended for use in children below 18 years of age.

#### Method of administration

Xarelto is for oral use.

The tablets can be taken with or without food (see sections 4.5 and 5.2).

#### Crushing of tablets

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.

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).

Concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month (see section 4.4).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

In ACS patients, efficacy and safety of Xarelto 2.5 mg twice daily have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine.

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 (see section 5.1).

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

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

##### **Haemorrhagic risk**

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. Therefore, the use of Xarelto in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

##### **Renal impairment**

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk.

Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Xarelto is to be used with caution (see section 4.5).

### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see sections 4.5 and 5.1).

Patients treated with Xarelto and antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk.

### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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

It should be used with caution in ACS and CAD/PAD patients:

- $\geq 75$  years of age if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine. The benefit-risk of the treatment should be individually assessed on a regular basis.
- with lower body weight ( $< 60$  kg) if co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine.
- CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with rivaroxaban (see section 5.1).

### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

### Patients with prior stroke and/or TIA

#### Patients with ACS

Xarelto 2.5 mg is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (see section 4.3). Few ACS patients with a prior stroke or TIA have been studied but the limited efficacy data available indicate that these patients do not benefit from treatment.

#### Patients with CAD/PAD

CAD/PAD patients with previous haemorrhagic or lacunar stroke, or an ischaemic, non-lacunar stroke with in the previous month were not studied (see section 4.3).

Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD with a previous stroke or TIA were not studied. Treatment with Xarelto 2.5 mg should be avoided in these patients receiving dual antiplatelet therapy.

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

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, 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 a patient is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xarelto should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Elderly population

Increasing age may increase haemorrhagic risk (see sections 5.1 and 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was



observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C<sub>trough</sub> of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

#### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-

feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

#### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

#### **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

<b>Indication</b>	<b>Number of patients*</b>	<b>Total daily dose</b>	<b>Maximum treatment duration</b>
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

Indication	Number of patients*	Total daily dose	Maximum treatment duration
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\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

**Table 2: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years*** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)

**Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

#### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

Rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific reversal agent (andexanet alfa) 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 rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and

aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative anti-factor-Xa tests (see section 5.2).

#### Clinical efficacy and safety

##### ACS

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of cardiovascular (CV) death, myocardial infarction (MI) or stroke in subjects with a recent ACS (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction [NSTEMI] or unstable angina [UA]). In the pivotal double-blind ATLAS ACS 2 TIMI 51 study, 15,526 patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups: rivaroxaban 2.5 mg orally twice daily, 5 mg orally twice daily or to placebo twice daily co-administered with ASA alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine). Patients with an ACS under the age of 55 had to have either diabetes mellitus or a previous MI. The median time on treatment was 13 months and overall treatment duration was up to almost 3 years. 93.2% of patients received ASA concomitantly plus thienopyridine treatment and 6.8% ASA only. Among patients receiving dual anti-platelets therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3% received prasugrel. Patients received the first dose of rivaroxaban at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.

Both the 2.5 mg twice daily and the 5 mg twice daily regimens of rivaroxaban were effective in further reducing the incidence of CV events on a background of standard antiplatelet care. The 2.5 mg twice daily regimen reduced mortality, and there is evidence that the lower dose had lower bleeding risks, therefore rivaroxaban 2.5 mg twice daily co-administered with acetylsalicylic acid (ASA) alone

or with ASA plus clopidogrel or ticlopidine is recommended for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers.

Relative to placebo, rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 4 and Figure 1). Also the first secondary endpoint (all-cause death, MI or stroke) was reduced significantly. An additional retrospective analysis showed a nominally significant reduction in the incidence rates of stent thrombosis compared with placebo (see Table 4). The incidence rates for the principal safety outcome (non-coronary artery bypass graft (CABG) TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo (see Table 6). However the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding.

In Table 5 the efficacy results of patients undergoing percutaneous coronary intervention (PCI) are presented. The safety results in this subgroup of patients undergoing PCI were comparable to the overall safety results.

Patients with elevated biomarkers (troponin or CK-MB) and without a prior stroke/TIA constituted 80% of the study population. The results of this patient population were also consistent with the overall efficacy and safety results.

**Table 4: Efficacy results from phase III ATLAS ACS 2 TIMI 51**

<b>Study population</b>	<b>Patients with a recent acute coronary syndrome <sup>a)</sup></b>	
<b>Treatment dose</b>	<b>Rivaroxaban 2.5 mg, twice daily, N=5,114 n (%) Hazard Ratio (HR) (95% CI) p-value <sup>b)</sup></b>	<b>Placebo N=5,113 n (%)</b>
Cardiovascular death, MI or stroke	313 (6.1%) 0.84 (0.72, 0.97) p = 0.020*	376 (7.4%)
All-cause death, MI or stroke	320 (6.3%) 0.83 (0.72, 0.97) p = 0.016*	386 (7.5%)
Cardiovascular death	94 (1.8%) 0.66 (0.51, 0.86) p = 0.002**	143 (2.8%)
All-cause death	103 (2.0%) 0.68 (0.53, 0.87) p = 0.002**	153 (3.0%)
MI	205 (4.0%) 0.90 (0.75, 1.09) p = 0.270	229 (4.5%)
Stroke	46 (0.9%) 1.13 (0.74, 1.73) p = 0.562	41 (0.8%)
Stent thrombosis	61 (1.2%) 0.70 (0.51, 0.97) p = 0.033**	87 (1.7%)

a) modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)

b) vs placebo; Log-Rank p-value

\* statistically superior

\*\* nominally significant



**Table 5: Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI**

<b>Study population</b>	<b>Patients with recent acute coronary syndrome undergoing PCI <sup>a)</sup></b>	
<b>Treatment dose</b>	<b>Rivaroxaban 2.5 mg, twice daily, N=3114 n (%) HR (95% CI) p-value <sup>b)</sup></b>	<b>Placebo N=3096 n (%)</b>
Cardiovascular death, MI or stroke	153 (4.9%) 0.94 (0.75, 1.17) p = 0.572	165 (5.3%)
Cardiovascular death	24 (0.8%) 0.54 (0.33, 0.89) p = 0.013**	45 (1.5%)
All-cause death	31 (1.0%) 0.64 (0.41, 1.01) p = 0.053	49 (1.6%)
MI	115 (3.7%) 1.03 (0.79, 1.33) p = 0.829	113 (3.6%)
Stroke	27 (0.9%) 1.30 (0.74, 2.31) p = 0.360	21 (0.7%)
Stent thrombosis	47 (1.5%) 0.66 (0.46, 0.95) p = 0.026**	71 (2.3%)

a) modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)

b) vs placebo; Log-Rank p-value

\*\* nominally significant

**Table 6: Safety results from phase III ATLAS ACS 2 TIMI 51**

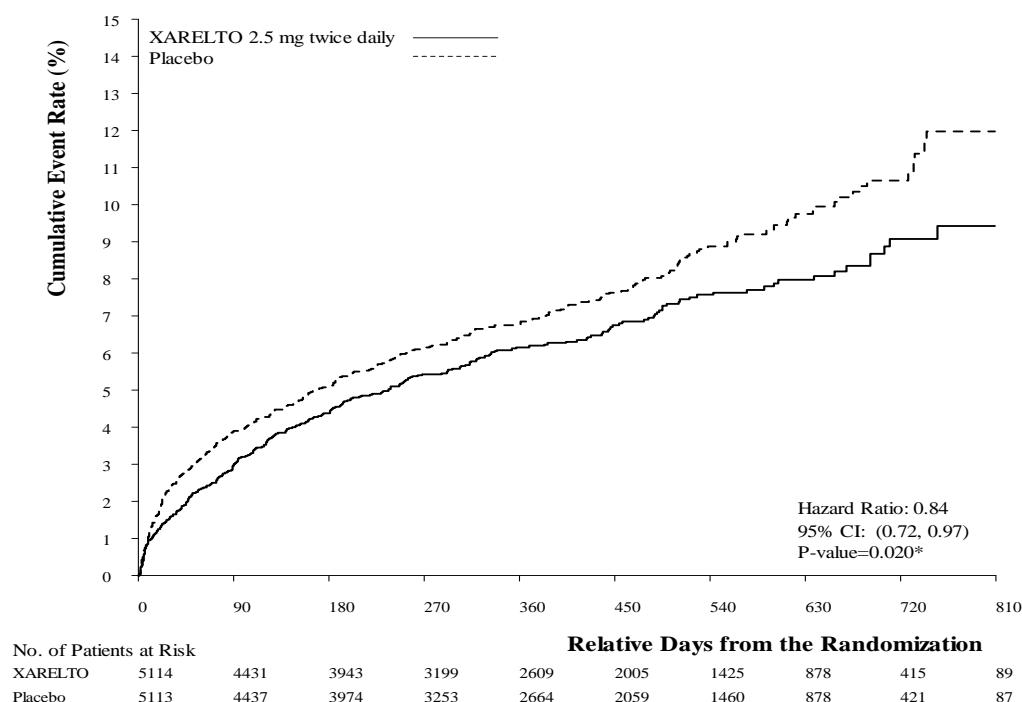
<b>Study population</b>	<b>Patients with recent acute coronary syndrome <sup>a)</sup></b>	
<b>Treatment dose</b>	<b>Rivaroxaban 2.5 mg, twice daily, N=5,115 n (%) HR (95% CI) p-value <sup>b)</sup></b>	<b>Placebo N=5,125 n(%)</b>
Non-CABG TIMI major bleeding event	65 (1.3%) 3.46 (2.08, 5.77) p = < 0.001*	19 (0.4%)
Fatal bleeding event	6 (0.1%) 0.67 (0.24, 1.89) p = 0.450	9 (0.2%)
Symptomatic intracranial haemorrhage	14 (0.3%) 2.83 (1.02, 7.86) p = 0.037	5 (0.1%)
Hypotension requiring treatment with intravenous inotropic agents	3 (0.1%)	3 (0.1%)
Surgical intervention for ongoing bleeding	7 (0.1%)	9 (0.2%)
Transfusion of 4 or more units of blood over a 48 hour period	19 (0.4%)	6 (0.1%)

a) safety population, on treatment

b) vs placebo; Log-Rank p-value

\* statistically significant

**Figure 1: Time to first occurrence of primary efficacy endpoint (CV death, MI or stroke)**



### CAD/PAD

The phase III COMPASS study (27,395 patients, 78.0% male, 22.0% female) demonstrated the efficacy and safety of rivaroxaban for the prevention of a composite of CV death, MI, stroke in patients with CAD or symptomatic PAD at high risk of ischaemic events. Patients were followed for a median of 23 months and maximum of 3.9 years.

Subjects without a continuous need for treatment with a proton pump inhibitor were randomised to pantoprazole or placebo. All patients were then randomised 1:1:1 to rivaroxaban 2.5 mg twice daily/ASA 100 mg once daily, to rivaroxaban 5 mg twice daily, or ASA 100 mg once daily alone, and their matching placebos.

CAD patients had multivessel CAD and/or prior MI. For patients < 65 years of age atherosclerosis involving at least two vascular beds or at least two additional cardiovascular risk factors were required.

PAD patients had previous interventions such as bypass surgery or percutaneous transluminal angioplasty or limb or foot amputation for arterial vascular disease or intermittent claudication with ankle/arm blood pressure ratio < 0.90 and/ or significant peripheral artery stenosis or previous carotid revascularisation or asymptomatic carotid artery stenosis  $\geq 50\%$ .

Exclusion criteria included the need for dual antiplatelet or other non-ASA antiplatelet or oral anticoagulant therapy and patients with high bleeding risk, or heart failure with ejection fraction < 30% or New York Heart Association class III or IV, or any ischaemic, non-lacunar stroke within 1 month or any history of haemorrhagic or lacunar stroke.

Rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily was superior to ASA 100 mg, in the reduction of the primary composite outcome of CV death, MI, stroke (see Table 7 and Figure 2).

There was a significant increase of the primary safety outcome (modified ISTH major bleeding events) in patients treated with rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 8).

For the primary efficacy outcome, the observed benefit of rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily compared with ASA 100 mg once daily was HR=0.89 (95% CI 0.7-1.1) in patients  $\geq 75$  years (incidence: 6.3% vs 7.0%) and HR=0.70 (95% CI 0.6-0.8) in patients  $< 75$  years (3.6% vs 5.0%). For modified ISTH major bleeding, the observed risk increase was HR=2.12 (95% CI 1.5-3.0) in patients  $\geq 75$  years (5.2% vs 2.5%) and HR=1.53 (95% CI 1.2-1.9) in patients  $< 75$  years (2.6% vs 1.7%).

The use of pantoprazole 40 mg once daily in addition to antithrombotic study medication in patients with no clinical need for a proton pump inhibitor showed no benefit in the prevention of upper gastrointestinal events (i.e. composite of upper gastrointestinal bleeding, upper gastrointestinal ulceration, or upper gastrointestinal obstruction or perforation); the incidence rate of upper gastrointestinal events was 0.39/100 patient-years in the pantoprazole 40 mg once daily group and 0.44/100 patient-years in the placebo once daily group.

**Table 7: Efficacy results from phase III COMPASS**

Study population	Patients with CAD/PAD <sup>a)</sup>					
Treatment dose	Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=9152		ASA 100 mg od N=9126			
	Patients with events	KM %	Patients with events	KM %	HR (95% CI)	p-value <sup>b)</sup>
Stroke, MI or CV death	379 (4.1%)	5.20%	496 (5.4%)	7.17%	0.76 (0.66;0.86)	p = 0.00004*
- Stroke	83 (0.9%)	1.17%	142 (1.6%)	2.23%	0.58 (0.44;0.76)	p = 0.00006
- MI	178 (1.9%)	2.46%	205 (2.2%)	2.94%	0.86 (0.70;1.05)	p = 0.14458
- CV death	160 (1.7%)	2.19%	203 (2.2%)	2.88%	0.78 (0.64;0.96)	p = 0.02053
All-cause mortality	313 (3.4%)	4.50%	378 (4.1%)	5.57%	0.82 (0.71;0.96)	
Acute limb ischaemia	22 (0.2%)	0.27%	40 (0.4%)	0.60%	0.55 (0.32;0.92)	

a) intention to treat analysis set, primary analyses

b) vs ASA 100 mg; Log-Rank p-value

\* The reduction in the primary efficacy outcome was statistically superior.

bid: twice daily; CI: confidence interval; KM %: Kaplan-Meier estimates of cumulative incidence risk calculated at 900 days; CV: cardiovascular; MI: myocardial infarction; od: once daily

**Table 8: Safety results from phase III COMPASS**

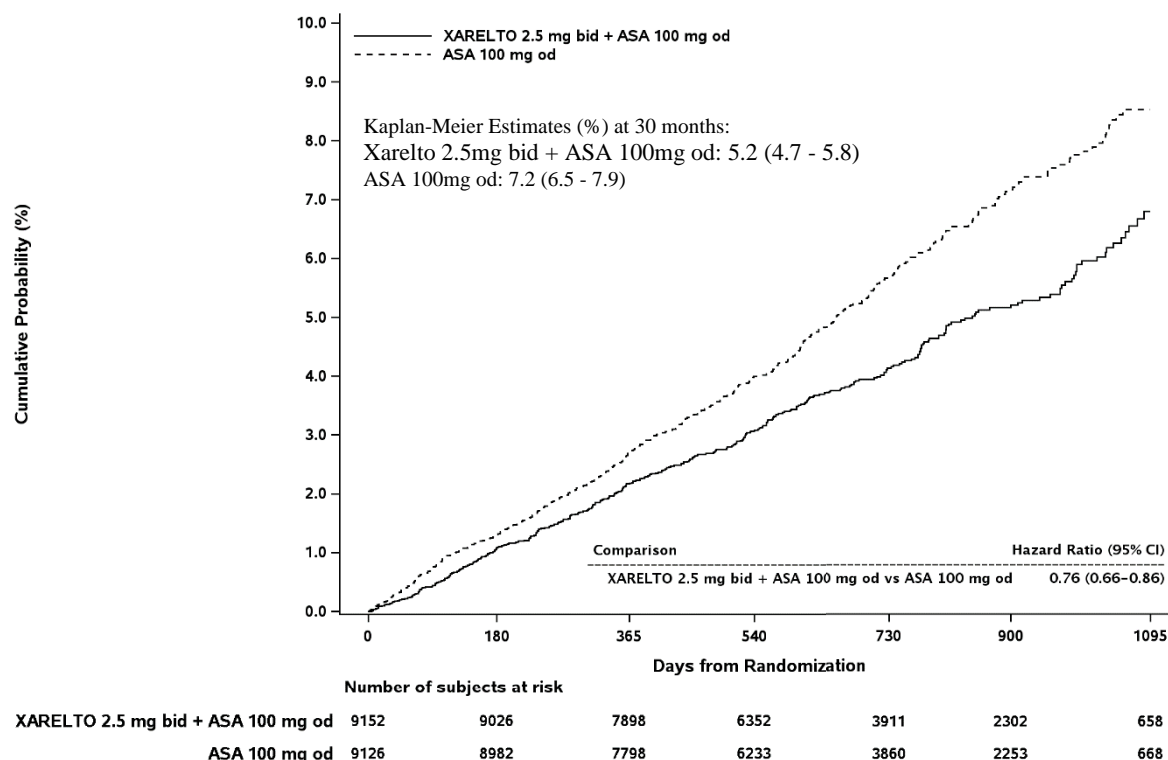
<b>Study population</b>	<b>Patients with CAD/PAD <sup>a)</sup></b>		
<b>Treatment dose</b>	<b>Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)</b>	<b>ASA 100 mg od N=9126 n (Cum.risk %)</b>	<b>Hazard Ratio (95 % CI)  p-value <sup>b)</sup></b>
Modified ISTH major bleeding	288 (3.9%)	170 (2.5%)	1.70 (1.40;2.05) p < 0.00001
- Fatal bleeding event	15 (0.2%)	10 (0.2%)	1.49 (0.67;3.33) p = 0.32164
- Symptomatic bleeding in critical organ (non-fatal)	63 (0.9%)	49 (0.7%)	1.28 (0.88;1.86) p = 0.19679
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	10 (0.1%)	8 (0.1%)	1.24 (0.49;3.14) p = 0.65119
- Bleeding leading to hospitalisation (non-fatal, not in critical organ, not requiring reoperation)	208 (2.9%)	109 (1.6%)	1.91 (1.51;2.41) p < 0.00001
- With overnight stay	172 (2.3%)	90 (1.3%)	1.91 (1.48;2.46) p < 0.00001
- Without overnight stay	36 (0.5%)	21 (0.3%)	1.70 (0.99;2.92) p = 0.04983
Major gastrointestinal bleeding	140 (2.0%)	65 (1.1%)	2.15 (1.60;2.89) p < 0.00001
Major intracranial bleeding	28 (0.4%)	24 (0.3%)	1.16 (0.67;2.00) p = 0.59858

a) intention-to-treat analysis set, primary analyses

b) vs ASA 100 mg; Log-Rank p-value

bid: twice daily; CI: confidence interval; Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months; ISTH: International Society on Thrombosis and Haemostasis; od: once daily

**Figure 2: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS**



bid: twice daily; od: once daily; CI: confidence interval

#### Patients after recent revascularisation procedure of the lower limb due to symptomatic PAD

In the pivotal phase III double-blind **VOYAGER PAD** trial, 6,564 patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were randomly assigned to one of two antithrombotic treatment groups: rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily, or to ASA 100 mg once daily, in a 1:1 fashion. Patients were allowed to additionally receive standard dose of clopidogrel once daily for up to 6 months. The objective of the study was to demonstrate the efficacy and safety of rivaroxaban plus ASA for the prevention of myocardial infarction, ischaemic stroke, CV death, acute limb ischaemia, or major amputation of a vascular etiology in patients after recent successful lower limb revascularisation procedures due to symptomatic PAD. Patients aged  $\geq 50$  years with documented moderate to severe symptomatic lower extremity atherosclerotic PAD evidenced by all of the following: clinically (i.e. functional limitations), anatomically (i.e. imaging evidence of PAD distal to external iliac artery) and haemodynamically (ankle-brachial-index [ABI]  $\leq 0.80$  or toe-brachial-index [TBI]  $\leq 0.60$  for patients without a prior history of limb revascularisation or ABI  $\leq 0.85$  or TBI  $\leq 0.65$  for patients with a prior history of limb revascularisation) were included. Patients in need of dual antiplatelet therapy for  $> 6$  months, or any additional antiplatelet therapy other than ASA and clopidogrel, or oral anticoagulant therapy, as well as patients with a history of intracranial haemorrhage, stroke, or TIA, or patients with eGFR  $< 15$  mL/min were excluded.

The mean duration of follow-up was 24 months and the maximum follow-up was 4.1 years. The mean age of the enrolled patients was 67 years and 17% of the patient population were  $> 75$  years. The median time from index revascularisation procedure to start of study treatment was 5 days in the overall population (6 days after surgical and 4 days after endovascular revascularisation including hybrid procedures). Overall, 53.0% of patients received short term background clopidogrel therapy with a median duration of 31 days. According to study protocol study treatment could be commenced as soon as possible but no later than 10 days after a successful qualifying revascularisation procedure and once hemostasis had been assured.

Rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily was superior in the reduction of the primary composite outcome of myocardial infarction, ischaemic stroke, CV death, acute limb ischaemia and major amputation of vascular etiology compared to ASA alone (see

Table 9). The primary safety outcome of TIMI major bleeding events was increased in patients treated with rivaroxaban and ASA, with no increase in fatal or intracranial bleeding (see Table 10). The secondary efficacy outcomes were tested in a prespecified, hierarchical order (see Table 9).

**Table 9: Efficacy results from phase III VOYAGER PAD**

<b>Study Population</b>	<b>Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD <sup>a)</sup></b>		
<b>Treatment Dosage</b>	<b>Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=3,286 n (Cum. risk %) <sup>c)</sup></b>	<b>ASA 100 mg od N=3,278 n (Cum. risk %) <sup>c)</sup></b>	<b>Hazard Ratio (95% CI) <sup>d)</sup></b>
<b>Primary efficacy outcome <sup>b)</sup></b>	<b>508 (15.5%)</b>	<b>584 (17.8%)</b>	<b>0.85 (0.76;0.96) p = 0.0043 <sup>e)*</sup></b>
- MI	131 (4.0%)	148 (4.5%)	0.88 (0.70;1.12)
- Ischaemic stroke	71 (2.2%)	82 (2.5%)	0.87 (0.63;1.19)
- CV death	199 (6.1%)	174 (5.3%)	1.14 (0.93;1.40)
- Acute limb ischaemia <sup>f)</sup>	155 (4.7%)	227 (6.9%)	0.67 (0.55;0.82)
- Major amputation of vascular etiology	103 (3.1%)	115 (3.5%)	0.89 (0.68;1.16)
<b>Secondary efficacy outcome</b>			
Unplanned index limb revascularisation for recurrent limb ischaemia	584 (17.8%)	655 (20.0%)	0.88 (0.79;0.99) p = 0.0140 <sup>e)*</sup>
Hospitalisation for a coronary or peripheral cause (either lower limb) of a thrombotic nature	262 (8.0%)	356 (10.9%)	0.72 (0.62;0.85) p < 0.0001 <sup>e)*</sup>
All-cause mortality	321 (9.8%)	297 (9.1%)	1.08 (0.92;1.27)
VTE events	25 (0.8%)	41 (1.3%)	0.61 (0.37;1.00)

<sup>a)</sup> intention to treat analysis set, primary analyses; ICAC adjudicated

<sup>b)</sup> composite of MI, ischaemic stroke, CV death (CV death and unknown cause of death), ALI, and major amputation of vascular etiology

<sup>c)</sup> only the first occurrence of the outcome event under analysis within the data scope from a subject is considered

<sup>d)</sup> HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use with treatment as the only covariate.

<sup>e)</sup> One sided p-value is based on the log-rank test stratified by type of procedure and clopidogrel use with treatment as factor.

<sup>f)</sup> acute limb ischaemia is defined as sudden significant worsening of limb perfusion, either with new pulse deficit or requiring therapeutic intervention (i.e. thrombolysis or thrombectomy, or urgent revascularisation), and leading to hospitalisation

\* The reduction in the efficacy outcome was statistically superior.

ALI: acute limb ischaemia; bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction; CV: cardiovascular; ICAC: Independent Clinical Adjudication Committee

**Table 10: Safety results from phase III VOYAGER PAD**

Study Population	Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD <sup>a)</sup>		
Treatment Dosage	Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=3,256 n (Cum. risk %) <sup>b)</sup>	ASA 100 mg od N=3,248 n (Cum. risk %) <sup>b)</sup>	Hazard Ratio (95% CI) <sup>c)</sup>  p-value <sup>d)</sup>
TIMI major bleeding (CABG / non-CABG)	62 (1.9%)	44 (1.4%)	1.43 (0.97;2.10) p = 0.0695
- Fatal bleeding	6 (0.2%)	6 (0.2%)	1.02 (0.33;3.15)
- Intracranial bleeding	13 (0.4%)	17 (0.5%)	0.78 (0.38;1.61)
- Overt bleeding associated with drop Hb $\geq 5\text{g/dL}$ / Hct $\geq 15\%$	46 (1.4%)	24 (0.7%)	1.94 (1.18;3.17)
ISTH major bleeding	140 (4.3%)	100 (3.1%)	1.42 (1.10;1.84) p = 0.0068
- Fatal bleeding	6 (0.2%)	8 (0.2%)	0.76 (0.26;2.19)
- Non-fatal critical organ bleeding	29 (0.9%)	26 (0.8%)	1.14 (0.67;1.93)
ISTH clinically relevant non-major bleeding	246 (7.6%)	139 (4.3%)	1.81 (1.47;2.23)

<sup>a)</sup> Safety analysis set (all randomised subjects with at least one dose of study drug), ICAC:

Independent Clinical Adjudication Committee

<sup>b)</sup> n = number of subjects with events, N = number of subjects at risk, % =  $100 * n/N$ , n/100p-yrs = ratio of number of subjects with incident events / cumulative at-risk time

<sup>c)</sup> HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use with treatment as the only covariate

<sup>d)</sup> Two sided p-value is based on the log rank-test stratified by type of procedure and clopidogrel use with treatment as a factor

#### CAD with heart failure

The **COMMANDER HF** study included 5,022 patients with heart failure and significant coronary artery disease (CAD) following a hospitalisation of decompensated heart failure (HF) which were randomly assigned into one of the two treatment groups: rivaroxaban 2.5 mg twice daily (N=2,507) or matching placebo (N=2,515), respectively. The overall median study treatment duration was 504 days. Patients must have had symptomatic HF for at least 3 months and left ventricular ejection fraction (LVEF) of  $\leq 40\%$  within one year of enrollment. At baseline, the median ejection fraction was 34% (IQR: 28%-38%) and 53% of subjects were NYHA Class III or IV.

The primary efficacy analysis (i.e. composite of all-cause mortality, MI, or stroke) showed no statistically significant difference between the rivaroxaban 2.5 mg twice daily group and the placebo group with a HR=0.94 (95% CI 0.84 - 1.05), p=0.270. For all-cause mortality, there was no difference between rivaroxaban and placebo in the number of events (event rate per 100 patient-years; 11.41 vs 11.63, HR: 0.98; 95% CI: 0.87 to 1.10; p=0.743). The event rates for MI per 100 patient-years (rivaroxaban vs placebo) were 2.08 vs 2.52 (HR 0.83; 95% CI: 0.63 to 1.08; p=0.165) and for stroke the event rates per 100 patient-years were 1.08 vs 1.62 (HR: 0.66; 95% CI: 0.47 to 0.95; p=0.023). The principal safety outcome (i.e. composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability), occurred in 18 (0.7%) patients in the rivaroxaban 2.5 mg twice daily treatment group and in 23 (0.9%) patients in the placebo group, respectively (HR=0.80; 95% CI 0.43 - 1.49; p=0.484). There was a statistically significant increase in ISTH major bleeding in the rivaroxaban group compared with placebo (event rate per 100 patient-years: 2.04 vs 1.21, HR 1.68; 95% CI: 1.18 to 2.39; p=0.003).

In patients with mild and moderate heart failure the treatment effects for the COMPASS study subgroup were similar to those of the entire study population (see section CAD/PAD).

### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food.

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

### Distribution

Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of



biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein). Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

### Special populations

#### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

#### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

#### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

#### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

#### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

### Pharmacokinetic data in patients

In patients receiving rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events in patients with ACS the geometric mean concentration (90% prediction interval) 2 - 4 h and about 12 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 47 (13 - 123) and 9.2 (4.4 - 18) mcg/l, respectively.

### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor-Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor-Xa activity was best described by an  $E_{\max}$  model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

### Paediatric population

Safety and efficacy have not been established in the indications ACS and CAD/PAD for children and adolescents up to 18 years.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Croscarmellose sodium  
Lactose monohydrate  
Hypromellose (2910)  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat

Macrogol (3350)  
Hypromellose (2910)  
Titanium dioxide (E 171)  
Iron oxide yellow (E 172)

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years

### Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

## **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

## **6.5 Nature and contents of container**

Cartons containing 14, 20, 28, 30, 56, 60, 98, 168 or 196 film-coated tablets in PP/Alu foil blisters.

Cartons containing 10 x 1 or 100 x 1 film-coated tablets in PP/Alu foil perforated unit dose blisters.

Multipacks containing 10 packs of 10 x 1 (100 film-coated tablets) in PP/Alu foil perforated unit dose blisters.

Cartons containing 14 film-coated tablets in PVC/PVDC/Alu foil blisters .

HDPE bottles with a PP screw cap containing 100 film-coated tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. Enteral feeding is not required immediately after administration of the 2.5 mg tablets.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/025-035, EU/1/08/472/041, EU/1/08/472/046-047

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008

Date of latest renewal: 22 May 2018

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 10 mg rivaroxaban.

### Excipient with known effect

Each film-coated tablet contains 26.51 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film-coated tablet (tablet)

Light red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and "10" and a triangle on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

### **4.2 Posology and method of administration**

#### Posology

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

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

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.

If a dose is missed the patient should take Xarelto immediately and then continue the following day with once daily intake as before.

##### *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg once daily, a dose of Xarelto 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	<b>Time period</b>	<b>Dosing schedule</b>	<b>Total daily dose</b>
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Xarelto for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), 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. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, 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.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is  $\leq 2.5$ .

When converting patients from VKAs to Xarelto, International Normalised Ratio (INR) values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. 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 testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

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

### *Special populations*

#### Renal impairment

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

- For the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30- 49 ml/min) (see section 5.2).
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).  
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).  
When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

#### Elderly population

No dose adjustment (see section 5.2)

#### Body weight

No dose adjustment (see section 5.2)

#### Gender

No dose adjustment (see section 5.2)

#### Paediatric population

The safety and efficacy of Xarelto 10 mg tablets in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto 10 mg tablets are not recommended for use in children below 18 years of age.

#### Method of administration

Xarelto is for oral use.

The tablets can be taken with or without food (see sections 4.5 and 5.2).

#### Crushing of tablets

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.

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

##### Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving Xarelto for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

##### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Xarelto is to be used with caution (see section 4.5).



#### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

#### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

#### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Hip fracture surgery

Rivaroxaban has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

#### Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

#### 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.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2).

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.

#### Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery

If an invasive procedure or surgical intervention is required, Xarelto 10 mg should be stopped at least 24 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 as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C<sub>max</sub>, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole,

voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{\text{trough}}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8).

Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

**Table 2: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years**** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)

**Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.



#### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

Rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific reversal agent (andexanet alfa) 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 rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and

aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15 s).

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

#### Clinical efficacy and safety

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

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of VTE, i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme.

Rivaroxaban 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.

In all three phase III studies (see table 4), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE and death) and major VTE (proximal DVT, non-fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

**Table 4: Efficacy and safety results from phase III clinical studies**

	<b>RECORD 1</b>			<b>RECORD 2</b>			<b>RECORD 3</b>		
<b>Study population</b>	<b>4,541 patients undergoing total hip replacement surgery</b>			<b>2,509 patients undergoing total hip replacement surgery</b>			<b>2,531 patients undergoing total knee replacement surgery</b>		
Treatment dose and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
Total VTE	18 (1.1%)	58 (3.7%)	< 0.001	17 (2.0%)	81 (9.3%)	< 0.001	79 (9.6%)	166 (18.9%)	< 0.001
Major VTE	4 (0.2%)	33 (2.0%)	< 0.001	6 (0.6%)	49 (5.1%)	< 0.001	9 (1.0%)	24 (2.6%)	0.01
Symptomatic VTE	6 (0.4%)	11 (0.7%)		3 (0.4%)	15 (1.7%)		8 (1.0%)	24 (2.7%)	
Major bleedings	6 (0.3%)	2 (0.1%)		1 (0.1%)	1 (0.1%)		7 (0.6%)	6 (0.5%)	

The analysis of the pooled results of the phase III studies corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

In addition to the phase III RECORD programme, a post-authorisation, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under real-life setting. Symptomatic VTE occurred in 57 (0.6%) patients in the rivaroxaban group (n=8,778) and 88 (1.0%) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomised studies.

#### *Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice). and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); Hazard Ratio (HR): 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 ((95% CI: 0.47 - 0.95), nominal  $p$  value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 5: Efficacy and safety results from phase III Einstein DVT**

Study population	<b>3,449 patients with symptomatic acute deep vein thrombosis</b>	
Treatment dose and duration	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=1,731</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=1,718</b>
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

In the Einstein PE study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p=0.0026$  (test for non-inferiority); HR: 1.123 (0.749 – 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 ((95% CI: 0.633 - 1.139), nominal  $p$  value  $p= 0.275$ ). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $p=0.082$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a HR 0.493 (95% CI: 0.308 - 0.789).

**Table 6: Efficacy and safety results from phase III Einstein PE**

<b>Study population</b>	<b>4,832 patients with an acute symptomatic PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=2,419</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=2,413</b>
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0026$  (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 – 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 7).

**Table 7: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

<b>Study population</b>	<b>8,281 patients with an acute symptomatic DVT or PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=4,150</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=4,131</b>
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 (<0.1%)	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 – 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a HR of 0.771 (95% CI: 0.614 – 0.967), nominal  $p$  value  $p = 0.0244$ .

In the Einstein Extension study (see Table 8) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a

non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 8: Efficacy and safety results from phase III Einstein Extension**

<b>Study population</b>	<b>1,197 patients continued treatment and prevention of recurrent venous thromboembolism</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 6 or 12 months N=602</b>	<b>Placebo 6 or 12 months N=594</b>
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (Table 9) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

**Table 9: Efficacy and safety results from phase III Einstein Choice**

Study population	<b>3,396 patients continued prevention of recurrent venous thromboembolism</b>		
Treatment dose	<b>Rivaroxaban 20 mg once daily N=1,107</b>	<b>Rivaroxaban 10 mg once daily N=1,127</b>	<b>ASA 100 mg once daily N=1,131</b>
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

\* p<0.001 (superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)

\*\* p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)

+ Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.44 (0.27–0.71), p=0.0009 (nominal)

++ Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.32 (0.18–0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively. These results in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

#### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and



anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%, apart from on the day of surgery and the following day when variability in exposure is high (70%).

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

### Distribution

Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption

rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

### Special populations

#### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

#### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

#### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

#### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

#### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

### Pharmacokinetic data in patients

In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7 - 273) and 14 (4 - 51) mcg/l, respectively.

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an  $E_{\max}$  model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

#### Paediatric population

Safety and efficacy have not been established in the indication primary prevention of VTE for children and adolescents up to 18 years.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Croscarmellose sodium  
Lactose monohydrate  
Hypromellose (2910)  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat

Macrogol (3350)  
Hypromellose (2910)  
Titanium dioxide (E 171)  
Iron oxide red (E 172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

#### Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Cartons containing 5, 10, 14, 28, 30 or 98 film-coated tablets in PP/Alu foil blisters.

Cartons containing 10 x 1 or 100 x 1 film-coated tablets in PP/Alu foil perforated unit dose blisters.

Multipacks containing 10 packs of 10 x 1 (100 film-coated tablets) in PP/Alu foil perforated unit dose blisters.

Cartons containing 5, 10 or 30 film-coated tablets in PVC/PVDC/Alu foil blisters .

HDPE bottles with a PP screw cap containing 100 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. Enteral feeding is not required immediately after administration of the 10 mg tablets.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/001-010, EU/1/08/472/022, EU/1/08/472/042-045.

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008

Date of latest renewal: 22 May 2018

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 15 mg rivaroxaban.

### Excipient with known effect

Each film-coated tablet contains 24.13 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Film-coated tablet (tablet)

Red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “15” and a triangle on the other side.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

#### Adults

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

#### Paediatric population

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

### **4.2 Posology and method of administration**

#### Posology

##### *Prevention of stroke and systemic embolism in adults*

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

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.

##### *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults*

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg once daily, a dose of Xarelto 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	<b>Time period</b>	<b>Dosing schedule</b>	<b>Total daily dose</b>
Treatment and prevention of recurrent DVT and PE	Day 1 - 21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Xarelto for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), 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. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, 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.

#### *Treatment of VTE and prevention of VTE recurrence in children and adolescents*

Xarelto treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1).

The dose for children and adolescent is calculated based on body weight.

- Body weight from 30 to 50 kg:  
a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight of 50 kg or more:  
a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Xarelto granules for oral suspension.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

- Prevention of stroke and systemic embolism:  
VKA treatment should be stopped and Xarelto therapy should be initiated when the International Normalised Ratio (INR) is  $\leq 3.0$ .
- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:  
VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is  $\leq 2.5$ .

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. 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 testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Paediatric patients:*

Children who convert from Xarelto to VKA need to continue Xarelto for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto. Co-administration of Xarelto and VKA is advised to continue until the INR is  $\geq 2.0$ . Once Xarelto is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

#### *Converting from parenteral anticoagulants to Xarelto*

For adult and paediatric patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

#### *Special populations*

##### Renal impairment

##### *Adults:*

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance  $< 15$  ml/min (see sections 4.4 and 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment the following dose recommendations apply:



- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).  
When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

#### Paediatric population:

- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m<sup>2</sup>): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>): Xarelto is not recommended as no clinical data is available (see section 4.4).

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2). No clinical data is available in children with hepatic impairment.

#### Elderly population

No dose adjustment (see section 5.2)

#### Body weight

No dose adjustment for adults (see section 5.2)

For paediatric patients the dose is determined based on body weight.

#### Gender

No dose adjustment (see section 5.2)

#### 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 (see sections 5.1 and 5.2). 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.

#### Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement

There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 - 49 ml/min]) in addition to a P2Y<sub>12</sub> inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

#### Paediatric population

The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

### Method of administration

#### *Adults*

Xarelto is for oral use.

The tablets are to be taken with food (see section 5.2).

#### Crushing of tablets

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. After the administration of crushed Xarelto 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

#### *Children and adolescents weighing 30 kg to 50 kg*

Xarelto is for oral use.

The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

#### Crushing of tablets

For patients who are unable to swallow whole tablets, Xarelto granules for oral suspension should be used.

If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.

The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

#### 4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

##### Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

##### *Paediatric population*

There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

##### Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Xarelto is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>), as no clinical data is available.

##### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

#### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

#### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/ transient ischaemic attack (TIA).

#### Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

#### 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. There is no clinical experience with the use of 15 mg rivaroxaban 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 and should be weighed against the urgency of a diagnostic procedure.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). 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.

No data is available on the timing of the placement or removal of neuraxial catheter in children while on Xarelto. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto 15 mg should be stopped at least 24 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 as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole,

voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{\text{trough}}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).



**Table 2: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years**** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)

**Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

### Paediatric population

#### *Treatment of VTE and prevention of VTE recurrence*

The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## **4.9 Overdose**

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (refer to the Summary of Product Characteristics of andexanet alfa).

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant 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 adults and in children receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged

from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

#### Paediatric population

PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L (see table 13 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

#### Clinical efficacy and safety

##### *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96;  $P < 0.001$  for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 - 1.03;  $P < 0.001$  for non-inferiority;  $P = 0.117$  for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 4. Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles ( $P = 0.74$  for interaction). Within the highest quartile according to centre, the Hazard Ratio (HR) with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 5).

**Table 4: Efficacy results from phase III ROCKET AF**

<b>Study population</b>	<b>ITT analyses of efficacy in patients with non-valvular atrial fibrillation</b>		
<b>Treatment dose</b>	<b>Rivaroxaban 20 mg once daily (15 mg once daily in patients with moderate renal impairment) Event rate (100 pt-yr)</b>	<b>Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)</b>	<b>HR (95% CI) p-value, test for superiority</b>
Stroke and non-CNS systemic embolism	269 (2.12)	306 (2.42)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51)	609 (4.81)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and myocardial infarction	659 (5.24)	709 (5.65)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99)	281 (2.22)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16)	27 (0.21)	0.74 (0.42 - 1.32) 0.308
Myocardial infarction	130 (1.02)	142 (1.11)	0.91 (0.72 - 1.16) 0.464

**Table 5: Safety results from phase III ROCKET AF**

Study population	Patients with non-valvular atrial fibrillation <sup>a)</sup>		
	<b>Rivaroxaban 20 mg once daily (15 mg once daily in patients with moderate renal impairment) Event rate (100 pt-yr)</b>	<b>Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)</b>	<b>HR (95% CI) p-value</b>
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96 - 1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment

\* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorisation, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean CHADS<sub>2</sub> score was 1.9 and HAS-BLED score was 2.0 in XANTUS, compared to a mean CHADS<sub>2</sub> and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years. These observations in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 162,000 patients from four countries, rivaroxaban was prescribed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The event rate for ischaemic stroke was 0.70 (95% CI 0.44 - 1.13) per 100 patient-years. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.43 (95% CI 0.31 - 0.59) for intracranial bleeding, 1.04 (95% CI 0.65 - 1.66) for gastrointestinal bleeding, 0.41 (95% CI 0.31 - 0.53) for urogenital bleeding and 0.40 (95% CI 0.25 - 0.65) for other bleeding.

#### *Patients undergoing cardioversion*

A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with



non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, myocardial infarction (MI) and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95% CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

#### *Patients with non-valvular atrial fibrillation who undergo PCI with stent placement*

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.

Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y<sub>12</sub> inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y<sub>12</sub> inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.

The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001, and HR 0.63; 95% CI 0.50-0.80; p<0.001, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.

The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

#### *Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 (95% CI: 0.47 - 0.95), nominal  $p$  value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 6: Efficacy and safety results from phase III Einstein DVT**

Study population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dose and duration	Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=1,731	Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=1,718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

In the Einstein PE study (see Table 7) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p=0.0026$  (test for non-inferiority); HR: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 (95% CI: 0.633 - 1.139), nominal  $p$  value  $p=0.275$ ). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $p=0.082$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a HR 0.493 (95% CI: 0.308 - 0.789).

**Table 7: Efficacy and safety results from phase III Einstein PE**

<b>Study population</b>	<b>4,832 patients with an acute symptomatic PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=2,419</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=2,413</b>
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0026$  (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 - 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 8).

**Table 8: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

<b>Study population</b>	<b>8,281 patients with an acute symptomatic DVT or PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=4,150</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=4,131</b>
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 (<0.1%)	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a HR of 0.771 (95% CI: 0.614 - 0.967), nominal p value  $p = 0.0244$ .

In the Einstein Extension study (see Table 9) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 9: Efficacy and safety results from phase III Einstein Extension**

<b>Study population</b>	<b>1,197 patients continued treatment and prevention of recurrent venous thromboembolism</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 6 or 12 months N=602</b>	<b>Placebo 6 or 12 months N=594</b>
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (see Table 10) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

**Table 10: Efficacy and safety results from phase III Einstein Choice**

<b>Study population</b>	<b>3,396 patients continued prevention of recurrent venous thromboembolism</b>		
<b>Treatment dose</b>	<b>Rivaroxaban 20 mg once daily N=1,107</b>	<b>Rivaroxaban 10 mg once daily N=1,127</b>	<b>ASA 100 mg once daily N=1,131</b>
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0 (0.0%)	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7%)	22 (2.0%)	20 (1.8%)

Study population	3,396 patients continued prevention of recurrent venous thromboembolism		
Treatment dose	Rivaroxaban 20 mg once daily N=1,107	Rivaroxaban 10 mg once daily N=1,127	ASA 100 mg once daily N=1,131
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%) <sup>+</sup>	17 (1.5%) <sup>++</sup>	53 (4.7%)

\* p<0.001 (superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)

\*\* p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)

+ Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)

++ Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.32 (0.18-0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively. These results in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

### Paediatric population

#### Treatment of VTE and prevention of VTE recurrence in paediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).

The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 11 and 12 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalisation of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165 patients in the comparator group. These findings were generally similar among age groups. There were 119 (36.2%) children with any treatment-emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

**Table 11: Efficacy results at the end of the main treatment period**

<b>Event</b>	<b>Rivaroxaban N=335*</b>	<b>Comparator N=165*</b>
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

\*FAS= full analysis set, all children who were randomised

**Table 12: Safety results at the end of the main treatment period**

	<b>Rivaroxaban N=329*</b>	<b>Comparator N=162*</b>
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

\* SAF= safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product.

The efficacy and safety profile of rivaroxaban was largely similar between the paediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

#### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

#### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

The following information is based on the data obtained in adults.

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is



released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

#### *Paediatric population*

Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food. Rivaroxaban 15 mg tablets should be taken with feeding or with food (see section 4.2).

#### Distribution

Plasma protein binding in adults is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

#### *Paediatric population*

No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available.  $V_{ss}$  estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

#### Biotransformation and elimination

In adults, of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

#### *Paediatric population*

No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives ( $t_{1/2}$ ) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in

children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5- < 2 years and less than 0.5 years, respectively.

### Special populations

#### *Gender*

In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

#### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

#### *Different weight categories*

In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

#### *Inter-ethnic differences*

In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

#### *Hepatic impairment*

Cirrhotic adult patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

No clinical data is available in children with hepatic impairment.

#### *Renal impairment*

In adults, there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>).

#### Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) mcg/l, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 13.

**Table 13: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age**

<b>Time intervals</b>								
<b>o.d.</b>	<b>N</b>	<b>12 - &lt; 18 years</b>	<b>N</b>	<b>6 - &lt; 12 years</b>				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
<b>b.i.d.</b>	<b>N</b>	<b>6 - &lt; 12 years</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
<b>t.i.d.</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>Birth - &lt; 2 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>	<b>N</b>	<b>Birth - &lt; 0.5 years</b>
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated

Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

#### Paediatric population

Safety and efficacy have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Croscarmellose sodium  
Lactose monohydrate  
Hypromellose (2910)  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat

Macrogol (3350)  
Hypromellose (2910)  
Titanium dioxide (E 171)  
Iron oxide red (E 172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

#### Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Cartons containing 10, 14, 28, 42 or 98 film-coated tablets in PP/Alu foil blisters.

Cartons containing 10 x 1 or 100 x 1 film-coated tablets in PP/Alu foil perforated unit dose blisters.

Multipacks containing 10 packs of 10 x 1 (100 film-coated tablets) in PP/Alu foil perforated unit dose blisters.

Cartons containing 14 film-coated tablets in PVC/PVDC/Alu foil blisters .

HDPE bottles with a PP screw cap containing 100 film-coated tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/011-016, EU/1/08/472/023, EU/1/08/472/036, EU/1/08/472/038, EU/1/08/472/048.

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008

Date of latest renewal: 22 May 2018

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## 1. NAME OF THE MEDICINAL PRODUCT

Xarelto 20 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg rivaroxaban.

### Excipient with known effect

Each film-coated tablet contains 21.76 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Brown-red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “20” and a triangle on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

#### Adults

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age  $\geq 75$  years, diabetes mellitus, prior stroke or transient ischaemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

#### Paediatric population

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

### 4.2 Posology and method of administration

#### Posology

##### *Prevention of stroke and systemic embolism in adults*

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Xarelto should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

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.

##### *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults*

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg once daily, a dose of Xarelto 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	<b>Time period</b>	<b>Dosing schedule</b>	<b>Total daily dose</b>
Treatment and prevention of recurrent DVT and PE	Day 1 - 21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Xarelto for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), 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. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, 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.

#### *Treatment of VTE and prevention of VTE recurrence in children and adolescents*

Xarelto treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1).

The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more:  
a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg:  
a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Xarelto granules for oral suspension.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

- Prevention of stroke and systemic embolism:  
VKA treatment should be stopped and Xarelto therapy should be initiated when the International Normalised Ratio (INR) is  $\leq 3.0$ .
  - Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:  
VKA treatment should be stopped and Xarelto therapy should be initiated once the INR is  $\leq 2.5$ .
- When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA.

Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. 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 testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Paediatric patients:*

Children who convert from Xarelto to VKA need to continue Xarelto for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto. Co-administration of Xarelto and VKA is advised to continue until the INR is  $\geq 2.0$ . Once Xarelto is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

#### *Converting from parenteral anticoagulants to Xarelto*

For adult and paediatric patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time the next Xarelto dose would be taken.

#### *Special populations*

##### Renal impairment

##### *Adults:*

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance  $< 15$  ml/min (see sections 4.4 and 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dose recommendations apply:



- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).  
When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

#### Paediatric population:

- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m<sup>2</sup>): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>): Xarelto is not recommended as no clinical data is available (see section 4.4).

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2). No clinical data is available in children with hepatic impairment.

#### Elderly population

No dose adjustment (see section 5.2)

#### Body weight

No dose adjustment for adults (see section 5.2)

For paediatric patients the dose is determined based on body weight.

#### Gender

No dose adjustment (see section 5.2)

#### 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 (see sections 5.1 and 5.2). 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.

#### Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement

There is limited experience of a reduced dose of 15 mg Xarelto once daily (or 10 mg Xarelto once daily for patients with moderate renal impairment [creatinine clearance 30 - 49 ml/min]) in addition to a P2Y<sub>12</sub> inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

#### Paediatric population

The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

### Method of administration

#### *Adults*

Xarelto is for oral use.

The tablets are to be taken with food (see section 5.2).

#### Crushing of tablets

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. After the administration of crushed Xarelto 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

#### *Children and adolescents weighing more than 50 kg*

Xarelto is for oral use.

The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

#### Crushing of tablets

For patients who are unable to swallow whole tablets, Xarelto granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.

The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

##### **Haemorrhagic risk**

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

##### ***Paediatric population***

There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

##### **Renal impairment**

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Xarelto is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>), as no clinical data is available.

##### **Interaction with other medicinal products**

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

#### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

#### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/transient ischaemic attack (TIA).

#### Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

#### 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. There is no clinical experience with the use of 20 mg rivaroxaban 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 and should be weighed against the urgency of a diagnostic procedure.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). 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.

No data is available on the timing of the placement or removal of neuraxial catheter in children while on Xarelto. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto 20 mg should be stopped at least 24 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 as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole,

voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{\text{trough}}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

## 4.8 Undesirable effects

### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).



**Table 2: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years**** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)

**Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

### Paediatric population

#### *Treatment of VTE and prevention of VTE recurrence*

The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

## **4.9 Overdose**

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (refer to the Summary of Product Characteristics of andexanet alfa).

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant 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 adults and in children receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged

from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

#### Paediatric population

PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L (see table 13 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

#### Clinical efficacy and safety

##### *Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96;  $P < 0.001$  for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 - 1.03;  $P < 0.001$  for non-inferiority;  $P = 0.117$  for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 4. Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles ( $P = 0.74$  for interaction). Within the highest quartile according to centre, the Hazard Ratio (HR) with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 5).

**Table 4: Efficacy results from phase III ROCKET AF**

<b>Study population</b>	<b>ITT analyses of efficacy in patients with non-valvular atrial fibrillation</b>		
<b>Treatment dose</b>	<b>Rivaroxaban 20 mg once daily (15 mg once daily in patients with moderate renal impairment) Event rate (100 pt-yr)</b>	<b>Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)</b>	<b>HR (95% CI) p-value, test for superiority</b>
Stroke and non-CNS systemic embolism	269 (2.12)	306 (2.42)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51)	609 (4.81)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and myocardial infarction	659 (5.24)	709 (5.65)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99)	281 (2.22)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16)	27 (0.21)	0.74 (0.42 - 1.32) 0.308
Myocardial infarction	130 (1.02)	142 (1.11)	0.91 (0.72 - 1.16) 0.464

**Table 5: Safety results from phase III ROCKET AF**

Study population	Patients with non-valvular atrial fibrillation <sup>a)</sup>		
	<b>Rivaroxaban 20 mg once daily (15 mg once daily in patients with moderate renal impairment) Event rate (100 pt-yr)</b>	<b>Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)</b>	<b>HR (95% CI) p-value</b>
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96 - 1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment

\* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorisation, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean CHADS<sub>2</sub> score was 1.9 and HAS-BLED score was 2.0 in XANTUS, compared to a mean CHADS<sub>2</sub> and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years. These observations in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 162,000 patients from four countries, rivaroxaban was prescribed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The event rate for ischaemic stroke was 0.70 (95% CI 0.44 - 1.13) per 100 patient-years. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.43 (95% CI 0.31 - 0.59) for intracranial bleeding, 1.04 (95% CI 0.65 - 1.66) for gastrointestinal bleeding, 0.41 (95% CI 0.31 - 0.53) for urogenital bleeding and 0.40 (95% CI 0.25 - 0.65) for other bleeding.

#### *Patients undergoing cardioversion*

A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted



VKA (randomised 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, myocardial infarction (MI) and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

#### *Patients with non-valvular atrial fibrillation who undergo PCI with stent placement*

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.

Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y<sub>12</sub> inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y<sub>12</sub> inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.

The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001, and HR 0.63; 95% CI 0.50-0.80; p<0.001, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.

The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

#### *Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until

the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and Rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 (95% CI: 0.47 - 0.95), nominal  $p$  value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 6: Efficacy and safety results from phase III Einstein DVT**

Study population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dose and duration	Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=1,731	Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=1,718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

<b>Study population</b>	<b>3,449 patients with symptomatic acute deep vein thrombosis</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=1,731</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=1,718</b>

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

In the Einstein PE study (see Table 7) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p=0.0026$  (test for non-inferiority); HR: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 (95% CI: 0.633 - 1.139), nominal  $p$  value  $p=0.275$ ). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $p=0.082$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a HR 0.493 (95% CI: 0.308 - 0.789).

**Table 7: Efficacy and safety results from phase III Einstein PE**

<b>Study population</b>	<b>4,832 patients with an acute symptomatic PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=2,419</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=2,413</b>
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 ( $<0.1\%$ )
Fatal PE/death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0026$  (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 - 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 8).

**Table 8: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

Study population	8,281 patients with an acute symptomatic DVT or PE	
Treatment dose and duration	Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=4,150	Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=4,131
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 ( $<0.1\%$ )	2 ( $<0.1\%$ )
Fatal PE/death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a HR of 0.771 ((95% CI: 0.614 - 0.967), nominal p value  $p = 0.0244$ ).

In the Einstein Extension study (see Table 9) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 9: Efficacy and safety results from phase III Einstein Extension**

Study population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dose and duration	Rivaroxaban <sup>a)</sup> 6 or 12 months N=602	Placebo 6 or 12 months N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (see Table 10) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

**Table 10: Efficacy and safety results from phase III Einstein Choice**

Study population	3,396 patients continued prevention of recurrent venous thromboembolism		
Treatment dose	Rivaroxaban 20 mg once daily N=1,107	Rivaroxaban 10 mg once daily N=1,127	ASA 100 mg once daily N=1,131
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0 (0.0%)	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

\* p<0.001 (superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)

\*\* p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)

+ Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)

++ Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.32 (0.18-0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively. These results in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

### Paediatric population

#### Treatment of VTE and prevention of VTE recurrence in paediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).

The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 11 and 12 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalisation of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165 patients in the comparator group. These findings were generally similar among age groups. There were 119 (36.2%) children with any treatment-emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

**Table 11: Efficacy results at the end of the main treatment period**

<b>Event</b>	<b>Rivaroxaban N=335*</b>	<b>Comparator N=165*</b>
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

\* FAS= full analysis set, all children who were randomised

**Table 12: Safety results at the end of the main treatment period**

	<b>Rivaroxaban N=329*</b>	<b>Comparator N=162*</b>
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

\* SAF = safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product

The efficacy and safety profile of rivaroxaban was largely similar between the paediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

#### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

### Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xarelto in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

## **5.2 Pharmacokinetic properties**

### Absorption

The following information is based on the data obtained in adults.

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

### Paediatric population

Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food. Rivaroxaban 20 mg tablets should be taken with feeding or with food (see section 4.2).

### Distribution

Plasma protein binding in adults is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.



### *Paediatric population*

No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available.  $V_{ss}$  estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

### Biotransformation and elimination

In adults, of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

### *Paediatric population*

No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives ( $t_{1/2}$ ) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

### Special populations

#### *Gender*

In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

#### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

#### *Different weight categories*

In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

#### *Inter-ethnic differences*

In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

### *Hepatic impairment*

Cirrhotic adult patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment.

There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

No clinical data is available in children with hepatic impairment.

### *Renal impairment*

In adults, there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively.

There are no data in patients with creatinine clearance < 15 ml/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>).

### Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) mcg/l, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 13.

**Table 13: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age**

<b>Time intervals</b>								
<b>o.d.</b>	<b>N</b>	<b>12 - &lt; 18 years</b>	<b>N</b>	<b>6 - &lt; 12 years</b>				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
<b>b.i.d.</b>	<b>N</b>	<b>6 - &lt; 12 years</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
<b>t.i.d.</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>Birth - &lt; 2 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>	<b>N</b>	<b>Birth - &lt; 0.5 years</b>
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated

Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

#### Paediatric population

Safety and efficacy have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Croscarmellose sodium  
Lactose monohydrate  
Hypromellose (2910)  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat

Macrogol (3350)  
Hypromellose (2910)  
Titanium dioxide (E 171)  
Iron oxide red (E 172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

#### Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Cartons containing 10, 14, 28 or 98 film-coated tablets in PP/Alu foil blisters.  
Cartons containing 10 x 1 or 100 x 1 film-coated tablets in PP/Alu foil perforated unit dose blisters.  
Multipacks containing 10 packs of 10 x 1 (100 film-coated tablets) in PP/Alu foil perforated unit dose blisters.  
Cartons containing 14 film-coated tablets in PVC/PVDC/Alu foil blisters .  
HDPE bottles with a PP screw cap containing 100 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration

of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

**7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/017-021, EU/1/08/472/024, EU/1/08/472/037, EU/1/08/472/039, EU/1/08/472/049.

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008  
Date of latest renewal: 22 May 2018

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

### **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets  
Xarelto 20 mg film-coated tablets

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 15 mg film-coated tablet contains 15 mg rivaroxaban.  
Each 20 mg film-coated tablet contains 20 mg rivaroxaban.

#### Excipient with known effect

Each 15 mg film-coated tablet contains 24.13 mg lactose (as monohydrate), see section 4.4.  
Each 20 mg film-coated tablet contains 21.76 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

### **3. PHARMACEUTICAL FORM**

Film-coated tablet (tablet)

15 mg film-coated tablet: red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “15” and a triangle on the other side.

20 mg film-coated tablet: brown-red, round biconvex tablets (6 mm diameter, 9 mm radius of curvature) marked with the BAYER-cross on one side and “20” and a triangle on the other side.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

#### **4.2 Posology and method of administration**

##### Posology

*Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE*

The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xarelto 10 mg once daily, a dose of Xarelto 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	<b>Time period</b>	<b>Dosing schedule</b>	<b>Total daily dose</b>
Treatment and prevention of recurrent DVT and PE	Day 1 - 21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

The 4-week treatment initiation pack of Xarelto is dedicated to patients who will transition from 15 mg twice daily to 20 mg once daily from Day 22 onwards (see section 6.5).

For patients with moderate or severe renal impairment where the decision has been taken for 15 mg once daily from Day 22 onwards, other pack sizes only containing 15 mg film-coated tablets are available (see dosing instructions in section “Special populations” below).

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), 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. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, 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.

#### *Converting from Vitamin K Antagonists (VKA) to Xarelto*

For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Xarelto therapy should be initiated once the International Normalised Ratio (INR) is  $\leq 2.5$ .

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

#### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is  $\geq 2.0$ . For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. 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 testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Xarelto 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

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

### *Special populations*

#### Renal impairment

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dose recommendations apply:

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg twice daily for the first 3 weeks.  
Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).  
When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (see section 5.2).

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

#### Elderly population

No dose adjustment (see section 5.2)

#### Body weight

No dose adjustment (see section 5.2)

#### Gender

No dose adjustment (see section 5.2)

#### Paediatric population

Xarelto treatment initiation pack should not be used in children aged 0 to 18 years because it is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

#### Method of administration

Xarelto is for oral use.

The tablets are to be taken with food (see section 5.2).

#### *Crushing of tablets*

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. After the administration of crushed Xarelto 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.



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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

#### **4.4 Special warnings and precautions for use**

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

##### Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

##### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). Xarelto should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

##### Interaction with other medicinal products

The use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and

P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

#### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

#### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

#### 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. There is no clinical experience with the use of 15 mg or 20 mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). 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.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto 15 mg/ Xarelto 20 mg should be stopped at least 24 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 as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent.

Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the

fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{\text{trough}}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

#### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

#### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8).

Patients experiencing these adverse reactions should not drive or use machines.

### **4.8 Undesirable effects**

#### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

**Table 2: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years**** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)

**Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		



Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

#### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

### **4.9 Overdose**

Rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific reversal agent (andexanet alfa) 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 rivaroxaban overdose may be considered.

#### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and

aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

#### Clinical efficacy and safety

##### *Treatment of DVT, PE and prevention of recurrent DVT and PE*

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range ( $\geq 2.0$ ). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 4) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p < 0.0001$  (test for non-inferiority); Hazard Ratio (HR): 0.680 (0.443 - 1.042),  $p=0.076$  (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 ((95% CI: 0.47 - 0.95), nominal  $p$  value  $p=0.027$ ) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $P=0.932$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

**Table 4: Efficacy and safety results from phase III Einstein DVT**

<b>Study population</b>	<b>3,449 patients with symptomatic acute deep vein thrombosis</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=1,731</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=1,718</b>
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

In the Einstein PE study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ( $p=0.0026$  (test for non-inferiority); HR: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 (95% CI: 0.633 - 1.139), nominal  $p$  value  $p=0.275$ ). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE ( $p=0.082$  for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a HR 0.493 (95% CI: 0.308 - 0.789).

**Table 5: Efficacy and safety results from phase III Einstein PE**

<b>Study population</b>	<b>4,832 patients with an acute symptomatic PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=2,419</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=2,413</b>
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 ( $<0.1\%$ )
Fatal PE/death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0026$  (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 - 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 6).

**Table 6: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE**

<b>Study population</b>	<b>8,281 patients with an acute symptomatic DVT or PE</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 3, 6 or 12 months N=4,150</b>	<b>Enoxaparin/VKA <sup>b)</sup> 3, 6 or 12 months N=4,131</b>
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 ( $<0.1\%$ )	2 ( $<0.1\%$ )
Fatal PE/death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

\*  $p < 0.0001$  (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a HR of 0.771 (95% CI: 0.614 - 0.967), nominal p value  $p = 0.0244$ .

In the Einstein Extension study (see Table 7) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

**Table 7: Efficacy and safety results from phase III Einstein Extension**

<b>Study population</b>	<b>1,197 patients continued treatment and prevention of recurrent venous thromboembolism</b>	
<b>Treatment dose and duration</b>	<b>Rivaroxaban <sup>a)</sup> 6 or 12 months N=602</b>	<b>Placebo 6 or 12 months N=594</b>
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

\*  $p < 0.0001$  (superiority), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (see Table 8) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

**Table 8: Efficacy and safety results from phase III Einstein Choice**

Study population	<b>3,396 patients continued prevention of recurrent venous thromboembolism</b>		
Treatment dose	<b>Rivaroxaban 20 mg once daily N=1,107</b>	<b>Rivaroxaban 10 mg once daily N=1,127</b>	<b>ASA 100 mg once daily N=1,131</b>
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0 (0.0%)	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

\* p<0.001 (superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)

\*\* p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)

+ Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)

++ Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.32 (0.18-0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively. These results in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

#### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and



anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

#### Paediatric population

Xarelto treatment initiation pack is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

## **5.2 Pharmacokinetic properties**

### Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

### Distribution

Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

### Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

### Special populations

#### *Gender*

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

#### *Elderly population*

Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

#### *Different weight categories*

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

#### *Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

#### *Hepatic impairment*

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

### Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) mcg/l, respectively.

### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an  $E_{\max}$  model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

### Paediatric population

Xarelto treatment initiation pack is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Tablet core

Microcrystalline cellulose  
Croscarmellose sodium  
Lactose monohydrate  
Hypromellose (2910)  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat

Macrogol (3350)  
Hypromellose (2910)  
Titanium dioxide (E 171)  
Iron oxide red (E 172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

#### Crushed tablets

Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

Treatment initiation pack for the first 4 weeks of treatment:

Wallet containing 49 film-coated tablets in PP/Aluminium foil blisters:

42 film-coated tablets of 15 mg and 7 film-coated tablets of 20 mg.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

#### Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/040

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008

Date of latest renewal: 22 May 2018

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 1 mg/mL granules for oral suspension

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

The granules contain 19.7 mg rivaroxaban per gram.

Each bottle contains 51.7 mg rivaroxaban or 103.4 mg rivaroxaban.

Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

### Excipient with known effect

Each mL of the reconstituted oral suspension contains 1.8 mg sodium benzoate (E 211), see section 4.4.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Granules for oral suspension

White granules

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

### **4.2 Posology and method of administration**

#### Posology

The dose and frequency of administration are determined based on body weight (see Table 1).

**Table 1: Recommended dose for Xarelto in paediatric patients from full-term neonates (following at least 10 days of oral feeding and weighing at least 2.6 kg) to children less than 18 years of age**

Bodyweight [kg]		Regimen Dose rivaroxaban			Total daily dose	Suitable blue syringe
		(1 mg rivaroxaban corresponds to 1 mL of the suspension)				
Min	Max	once a day	2 times a day	3 times a day		
2.6	< 3			0.8 mg	2.4 mg	1 mL
3	< 4			0.9 mg	2.7 mg	1 mL
4	< 5			1.4 mg	4.2 mg	5 mL
5	< 7			1.6 mg	4.8 mg	5 mL
7	< 8			1.8 mg	5.4 mg	5 mL
8	< 9			2.4 mg	7.2 mg	5 mL
9	< 10			2.8 mg	8.4 mg	5 mL
10	< 12			3.0 mg	9.0 mg	5 mL
12	< 30	5 mg			10 mg	5 mL or 10 mL
30	< 50	15 mg			15 mg	10 mL
≥ 50		20 mg			20 mg	10 mL

The weight of the child should be monitored and the dose reviewed regularly, especially for children below 12 kg. This is to ensure that a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

*Frequency of dosing:*

- *For a once a day regimen*  
The doses should be taken approximately 24 hours apart.
- *For a two times a day regimen*  
The doses should be taken approximately 12 hours apart.
- *For a three times a day regimen*  
The doses should be taken approximately 8 hours apart.

For patients with body weight of at least 2.6 kg to less than 30 kg only the oral suspension should be used. Do not split Xarelto tablets or use Xarelto tablets of lower strength in an attempt to provide doses for children with body weight below 30 kg.

For patients with body weight of at least 30 kg, Xarelto oral suspension or tablets of 15 mg or 20 mg strength can be administered once a day.

Xarelto oral suspension is provided with either 1 mL or 5 mL and 10 mL blue syringes (oral dosing syringe) with their adapter. To ensure accurate dosing it is recommended to use the blue syringes as follows (see Table 1):

- 1 mL blue syringe (with 0.1 mL graduations) must be used in patients weighing less than 4 kg
- 5 mL blue syringe (with 0.2 mL graduations) may be used in patients weighing 4 kg up to less than 30 kg
- 10 mL blue syringe (with 0.5 mL graduations) is only recommended for use in patients weighing 12 kg or more

For patients weighing 12 kg up to less than 30 kg, either 5 mL or 10 mL blue syringes can be used. It is recommended that the healthcare professional advises the patient or caregiver which blue syringe to use to ensure that the correct volume is administered.

Instructions for Use booklet is provided with the medicinal product.

*Initiation of treatment*

- *Paediatric patients from term neonates to less than 6 months*  
Treatment for paediatric patients from term neonates to less than 6 months of age, who at birth had at least 37 weeks of gestation, weigh at least 2.6 kg, and have had at least 10 days of oral feeding should be initiated following at least 5 days of initial parenteral anticoagulation

treatment (see sections 4.4 and 5.1). Xarelto is dosed based on body weight using the oral suspension formulation (see Table 1).

- *Paediatric patients from 6 months of age to less than 18 years*  
Treatment for paediatric patients from 6 months to less than 18 years of age should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1). Xarelto is dosed based on body weight (see Table 1).

#### *Duration of treatment*

- *All children, except those aged less than 2 years with catheter-related thrombosis*  
Therapy should be continued for at least 3 months. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.
- *Children aged less than 2 years with catheter-related thrombosis*  
Therapy should be continued for at least 1 month. Treatment can be extended up to 3 months when clinically necessary. The benefit-risk of continued therapy after 1 month should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

#### *Missed doses*

- *Once a day regimen*  
If taken once a day, a missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.
- *Two times a day regimen*  
If taken twice a day, a missed morning dose should be taken immediately when it is noticed, and it may be taken together with the evening dose. A missed evening dose can only be taken during the same evening, the patient should not take two doses the next morning.
- *Three times a day regimen*  
If taken three times a day, the three times daily administration schedule with approximately 8-hour intervals should simply be resumed at the next scheduled dose without compensating for the missed dose.

On the following day, the child should continue with the regular once, twice or three times daily regimen.

#### *Converting from parenteral anticoagulants to Xarelto*

For patients currently receiving a parenteral anticoagulant, start Xarelto 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal product (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

#### *Converting from Xarelto to parenteral anticoagulants*

Discontinue Xarelto and give the first dose of parenteral anticoagulant at the time that the next Xarelto dose would be taken.

#### *Converting from Vitamin K antagonists (VKA) to Xarelto*

VKA treatment should be stopped and Xarelto therapy should be initiated once the International Normalised Ratio (INR) is  $\leq 2.5$ .

When converting patients from VKAs to Xarelto, INR values will be falsely elevated after the intake of Xarelto. The INR is not valid to measure the anticoagulant activity of Xarelto, and therefore should not be used (see section 4.5).

### *Converting from Xarelto to Vitamin K antagonists (VKA)*

There is a potential for inadequate anticoagulation during the transition from Xarelto to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xarelto can contribute to an elevated INR.

Children who convert from Xarelto to VKA need to continue Xarelto for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xarelto. Co-administration of Xarelto and VKA is advised to continue until the INR is  $\geq 2.0$ . Once Xarelto is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

### *Special populations*

#### Renal impairment

- Children 1 year or older with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m<sup>2</sup>): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m<sup>2</sup>): Xarelto is not recommended as no clinical data is available (see section 4.4).
- Children below 1 year: the renal function should only be determined using serum creatinine. Xarelto is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile (see Table 2), as no data are available (see section 4.4).

**Table 2: Reference values of serum creatinine in children younger than 1 year of age (Boer et al, 2010)**

Age	97.5 <sup>th</sup> percentile of creatinine (µmol/L )	97.5 <sup>th</sup> percentile of creatinine (mg/dL )
Day 1	81	0.92
Day 2	69	0.78
Day 3	62	0.70
Day 4	58	0.66
Day 5	55	0.62
Day 6	53	0.60
Day 7	51	0.58
Week 2	46	0.52
Week 3	41	0.46
Week 4	37	0.42
Month 2	33	0.37
Month 3	30	0.34
Month 4–6	30	0.34
Month 7–9	30	0.34
Month 10–12	32	0.36

#### Hepatic impairment

No clinical data is available in children with hepatic impairment.

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 4.3 and 5.2).

#### Body weight

For children the dose is determined based on body weight (see Posology above).

#### Gender

No dose adjustment (see section 5.2)



#### Paediatric population

The safety and efficacy of Xarelto in children aged 0 to < 18 years have not been established in indications other than treatment of venous thromboembolism (VTE) and prevention of VTE recurrence. No or insufficient data are available for other indications (see also section 5.1). Therefore, Xarelto is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

#### Method of administration

Xarelto is for oral use.

The oral suspension should be taken with feeding or with food (see section 5.2).

For details on preparation and administration of the oral suspension see section 6.6.

The oral suspension may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

Each dose should be immediately followed by the intake of one typical serving of liquid. This typical serving may include liquid volume used for feeding.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering it orally (see sections 5.2 and 6.6).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

### **4.4 Special warnings and precautions for use**

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Dosing of rivaroxaban cannot be reliably determined in the following patient populations and was not studied. It is therefore not recommended in children less than 6 months of age who:

- at birth had less than 37 weeks of gestation, or
- have a body weight of less than 2.6 kg, or
- had less than 10 days of oral feeding.

#### Haemorrhagic risk

As with other anticoagulants, patients taking Xarelto are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xarelto administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequent during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at an increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

#### Renal impairment

Xarelto is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate  $< 50 \text{ mL/min/1.73 m}^2$ ), as no clinical data is available.

Xarelto is not recommended in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

#### Interaction with other medicinal products

No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp.

Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

#### Patients with cancer

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

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated (see section 4.3).

#### Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that this medicinal product provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with antiphospholipid syndrome

Direct acting oral anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

#### Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Xarelto have not been established in these clinical situations.

#### Spinal/epidural anaesthesia or lumbar 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. There is no clinical experience with the use of rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or lumbar 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 and should be weighed against the urgency of a diagnostic procedure.

No data is available on the timing of the placement or removal of neuraxial catheter in children while on Xarelto. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

#### Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Xarelto should be stopped at least 24 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 as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

#### Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

#### Information about excipients

Xarelto granules for oral suspension contains 1.8 mg sodium benzoate (E 211) in each mL oral suspension. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn infants (up to 4 weeks old). Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

This medicinal product contains less than 1 mmol sodium (23 mg) per millilitre, that is to say essentially “sodium-free”.

### **4.5 Interaction with other medicinal products and other forms of interaction**

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

#### CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in  $C_{max}$ . The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.

In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in  $C_{max}$  when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean  $C_{max}$ . The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

#### Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

#### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

#### SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

#### Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the  $C_{trough}$  of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

#### CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

#### Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

#### Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

### **4.6 Fertility, pregnancy and lactation**

#### Pregnancy

Safety and efficacy of Xarelto have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3).

Female adolescents of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

#### Breast-feeding

Safety and efficacy of Xarelto have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

#### Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

### **4.7 Effects on ability to drive and use machines**

Xarelto has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

### **4.8 Undesirable effects**

#### Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 3).

Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

**Table 3: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies**

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

\* Patients exposed to at least one dose of rivaroxaban

\*\* From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and ‘Description of selected adverse reactions’ below) (Table 4). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

**Table 4: Bleeding\* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies**

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years <sup>#</sup>	0.74 per 100 patient years**** <sup>#</sup>

\* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.

\*\* In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied

\*\*\* A selective approach to adverse event collection was applied

# From the VOYAGER PAD study

#### Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto in adult and paediatric patients are summarised in Table 5 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

very common ( $\geq 1/10$ )

common ( $\geq 1/100$  to  $< 1/10$ )

uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

very rare ( $< 1/10,000$ )

not known (cannot be estimated from the available data)



**Table 5: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use\* and in two phase II and two phase III studies in paediatric patients**

Common	Uncommon	Rare	Very rare	Not known
<b>Blood and lymphatic system disorders</b>				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) <sup>A</sup> , thrombocytopenia			
<b>Immune system disorders</b>				
	Allergic reaction, dermatitis allergic, angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
<b>Nervous system disorders</b>				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
<b>Eye disorders</b>				
Eye haemorrhage (incl. conjunctival haemorrhage)				
<b>Cardiac disorders</b>				
	Tachycardia			
<b>Vascular disorders</b>				
Hypotension, haematoma				
<b>Respiratory, thoracic and mediastinal disorders</b>				
Epistaxis, haemoptysis				
<b>Gastrointestinal disorders</b>				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth			
<b>Hepatobiliary disorders</b>				
Increase in transaminases	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased GGT <sup>A</sup>	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)		

Common	Uncommon	Rare	Very rare	Not known
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome	
<b>Musculoskeletal and connective tissue disorders</b>				
Pain in extremity <sup>A</sup>	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia <sup>B</sup> ), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
<b>General disorders and administration site conditions</b>				
Fever <sup>A</sup> , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema <sup>A</sup>		
<b>Investigations</b>				
	Increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup>			
<b>Injury, poisoning and procedural complications</b>				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion <sup>A</sup>		Vascular pseudoaneurysm <sup>C</sup>		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

\* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

### Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xarelto may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

### Paediatric patients

#### *Treatment of VTE and prevention of VTE recurrence*

The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the [national reporting system](#) listed in [Appendix V](#).

## **4.9 Overdose**

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”). There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however no data is available at supratherapeutic doses in children.

A specific reversal agent antagonising the pharmacodynamic effect of rivaroxaban is not established in children.

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

### Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours in adults. The half-life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these medicinal products in adults and in children receiving rivaroxaban (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

#### Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

#### Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to

reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in routine clinical practice. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

### Paediatric population

PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L (see Table 8 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

### Clinical efficacy and safety

#### *Treatment of VTE and prevention of VTE recurrence in paediatric patients*

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).

The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and

safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 6 and 7 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalisation of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165 patients in the comparator group. These findings were generally similar among age groups. There were 119 (36.2%) children with any treatment-emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

**Table 6: Efficacy results at the end of the main treatment period**

<b>Event</b>	<b>Rivaroxaban N=335*</b>	<b>Comparator N=165*</b>
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

\* FAS = full analysis set, all children who were randomised

**Table 7: Safety results at the end of the main treatment period**

	<b>Rivaroxaban N=329*</b>	<b>Comparator N=162*</b>
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

\* SAF = safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product

The efficacy and safety profile of rivaroxaban was largely similar between the paediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

### *Thromboprophylaxis in Paediatric Patients with Congenital Heart Disease after the Fontan Procedure*

The efficacy and safety of rivaroxaban for thromboprophylaxis in 110 paediatric patients with congenital heart disease who have undergone the Fontan procedure within 4 months prior to enrolment was evaluated in a prospective, open-label, 2-part (part B active-controlled) study (UNIVERSE) where rivaroxaban was used for thromboprophylaxis for 12 months compared with acetylsalicylic acid in children 2 to 8 years of age with single ventricle physiology who had the Fontan procedure. Patients received either body weight-adjusted doses of rivaroxaban ([n=76], exposures to match that of 10 mg daily dose in adults) or acetylsalicylic acid ([n=34] approximately 5 mg/kg). The dosing studied in UNIVERSE for thromboprophylaxis was thus lower and cannot be derived from the approved paediatric dose for the treatment of VTE.

Few thromboembolic events were observed in the UNIVERSE study (rivaroxaban group (1 [1.6%]) vs acetylsalicylic acid group (3 [8.8%])) and the amount of bleeding events was similar between study arms with 5 (7.8%) clinically relevant bleedings (including 1 major) in the rivaroxaban group versus 3 (8.8%; none of which major) in the acetylsalicylic acid group.

### Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomised open-label multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

## **5.2 Pharmacokinetic properties**

### Absorption

The following information is based on the data obtained in adults.

Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability.

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

Bioequivalence was demonstrated for the granules for oral suspension formulation compared to the marketed tablet at the 10 mg dose in fasted state as well as for the 20 mg dose in fed state.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and  $C_{max}$  compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and  $C_{max}$ ) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube

followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

#### *Paediatric population*

Children received a rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as a tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children is available so the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food. Rivaroxaban oral suspension should be taken with feeding or with food (see section 4.2).

#### Distribution

Plasma protein binding in adults is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with  $V_{ss}$  being approximately 50 litres.

#### *Paediatric population*

No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available.  $V_{ss}$  estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

#### Biotransformation and elimination

In adults, of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

#### *Paediatric population*

No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives ( $t_{1/2}$ ) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

#### Special populations

##### *Hepatic impairment*

No clinical data is available in children with hepatic impairment. In adults, cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban



pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

#### *Renal impairment*

No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate  $< 50 \text{ mL/min/1.73 m}^2$ ) or in children younger than 1 year with serum creatinine results above 97.5th percentile (see section 4.4).

In adults, there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 mL/min), moderate (creatinine clearance 30 - 49 mL/min) and severe (creatinine clearance 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance  $< 15 \text{ mL/min}$ .

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

#### *Gender*

In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

#### *Different weight categories*

In adults, extremes in body weight ( $< 50 \text{ kg}$  or  $> 120 \text{ kg}$ ) had only a small influence on rivaroxaban plasma concentrations (less than 25%). In children, rivaroxaban is dosed based on body weight. An exploratory analysis in children did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure.

#### *Inter-ethnic differences*

In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

#### Pharmacokinetic data in patients

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 8.

**Table 8: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age**

<b>Time intervals</b>								
<b>o.d.</b>	<b>N</b>	<b>12 - &lt; 18 years</b>	<b>N</b>	<b>6 - &lt; 12 years</b>				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
<b>b.i.d.</b>	<b>N</b>	<b>6 - &lt; 12 years</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
<b>t.i.d.</b>	<b>N</b>	<b>2 - &lt; 6 years</b>	<b>N</b>	<b>Birth - &lt; 2 years</b>	<b>N</b>	<b>0.5 - &lt; 2 years</b>	<b>N</b>	<b>Birth - &lt; 0.5 years</b>
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated

Values below lower limit of quantification (LLOQ) were substituted by ½ LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

#### Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E<sub>max</sub> model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/L). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

### **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Citric acid, anhydrous (E 330)

Hypromellose (2910)

Mannitol (E 421)

Microcrystalline cellulose and carmellose sodium

Sodium benzoate (E 211)

Sucralose (E 955)

Xanthan gum (E 415)

Flavour sweet and creamy: flavouring substances, maltodextrin (maize), propylene glycol (E 1520) and acacia gum (E 414).

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

After reconstitution the suspension is stable for 14 days.

### 6.4 Special precautions for storage

Do not store above 30 °C.

Do not freeze.

Store the prepared suspension upright.

### 6.5 Nature and contents of container

Xarelto 1 mg/mL granules for oral suspension is packed in a folding box containing:

- For children weighing **less than 4 kg**:
  - 2.625 g granules, corresponding to 51.7 mg rivaroxaban, in 1 brown glass bottle 100 mL, closed with a child resistant screw cap
  - 2 blue syringes 1 mL with 0.1 mL marked graduations
  - 1 adapter for bottles and blue syringes
  - 1 water syringe 50 mL with 1 mL marked graduations

or

- For children weighing **4 kg and more**:
  - 5.25 g granules, corresponding to 103.4 mg rivaroxaban, in 1 brown glass bottle 250 mL, closed with a child resistant screw cap
  - 2 blue syringes 5 mL with 0.2 mL marked graduations
  - 2 blue syringes 10 mL with 0.5 mL marked graduations
  - 1 adapter for bottles and blue syringes
  - 1 water syringe 100 mL with 2 mL marked graduations

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### Suspension

Before administration the granules must be suspended into a homogenous suspension with non-carbonated water giving a final concentration of 1 mg per mL.

The amount of water to be used is:

- 50 mL for the 100 mL bottle containing 2.625 g granules
- 100 mL for the 250 mL bottle containing 5.25 g granules

The bottle has to be shaken after reconstitution for 60 seconds and before each dose for 10 seconds.

After reconstitution the medicinal product is a white to off-white suspension.

For dose administration after reconstitution, the blue syringes (1 mL, 5 mL or 10 mL) are provided (see section 4.2, Table 1).

Complete details on preparation and administration of the oral suspension can be found in the Instructions for Use that is provided with the medicinal product or in an educational video which can be accessed via QR code displayed on the Patient Alert Card that is also provided with the medicinal product.

The suspension may be given through a nasogastric or gastric feeding tube. Gastric placement of the tube should be confirmed before administering Xarelto. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration, the feeding tube should be flushed with water. This should then be immediately followed by nasogastric or gastric feeding.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/050-051

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 30 September 2008

Date of latest renewal: 22 May 2018

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## **A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer responsible for batch release

Bayer AG  
Kaiser-Wilhelm-Allee  
51368 Leverkusen  
Germany

Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy

Bayer Bitterfeld GmbH  
Ortsteil Greppin, Salegaster Chaussee 1  
06803 Bitterfeld-Wolfen  
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## **B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

## **C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## **D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Xarelto. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III]
- Patient Alert Cards (Xarelto granules for oral suspension) [Text included in Annex III]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
  - The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.
- That all parents/caregivers of paediatric patients and all paediatric patients administered Xarelto granules for oral suspension should be counselled about:
  - reconstitution and dosing of the oral suspension

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III.

To ensure correct reconstitution and handling of Xarelto granules for oral suspension, a training video for healthcare providers and caregivers will be made available by the MAH electronically on company webpages (as per local country requirements). The MAH shall send notifications to potential prescribers in line with the communication plan agreed with the national competent authority detailing the location of the training video, the necessity of training and the documentation of training.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**



## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON FOR 2.5 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 2.5 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

14 film-coated tablets  
20 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
56 film-coated tablets  
60 film-coated tablets  
98 film-coated tablets  
168 film-coated tablets  
196 film-coated tablets  
10 x 1 film-coated tablets  
100 x 1 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/025	14 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/026	28 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/027	56 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/028	60 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/029	98 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/030	168 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/031	196 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/032	10 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/033	100 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/035	30 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/041	20 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/047	14 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 2.5 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX) FOR 2.5 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 2.5 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 100 (10 packs of 10 x 1) film-coated tablets.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/034 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 2.5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) FOR 2.5 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 2.5 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 x 1 film-coated tablets.  
Component of a multipack, can't be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/034 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 2.5 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**



<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>UNIT DOSE BLISTER (10 x 1 TABLETS) FOR 2.5 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 2.5 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 10 TABLETS FOR 2.5 MG</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 2.5 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF 14 TABLETS FOR 2.5 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg tablets  
rivaroxaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Bayer (logo)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.

*sun as symbol*  
*moon as symbol*

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 2.5 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 2.5 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 2.5 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/046      100 film-coated tablets      (HDPE Bottle)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription. (only applicable for bottle label, not applicable for outer carton)

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 2.5 mg (only applicable for outer carton, not applicable for bottle label)

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC (only applicable for outer carton, not applicable for bottle label)  
SN (only applicable for outer carton, not applicable for bottle label)  
NN (only applicable for outer carton, not applicable for bottle label)

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON FOR 10 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 10 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 film-coated tablets  
10 film-coated tablets  
14 film-coated tablets  
28 film-coated tablets  
30 film-coated tablets  
98 film-coated tablets  
10 x 1 film-coated tablets  
100 x 1 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Bayer AG  
51368 Leverkusen  
Germany

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/08/472/001	5 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)
EU/1/08/472/002	10 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)
EU/1/08/472/003	30 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)
EU/1/08/472/004	100 x 1 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)
EU/1/08/472/005	5 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/006	10 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/007	30 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/008	100 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/009	10 x 1 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)
EU/1/08/472/010	10 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/042	14 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/043	28 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/044	98 film-coated tablets	(PP/Aluminium foil blisters)

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

Xarelto 10 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX) FOR 10 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 10 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 100 (10 packs of 10 x 1) film-coated tablets.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/022 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 10 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) FOR 10 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 10 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 x 1 film-coated tablets.  
Component of a multipack, can't be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/022 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xarelto 10 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 10 TABLETS FOR 10 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 10 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 14 TABLETS FOR 10 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 10 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
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EXP

<b>4. BATCH NUMBER</b>
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Lot

<b>5. OTHER</b>
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Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 10 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 10 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/045      100 film-coated tablets      (HDPE Bottle)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription. (only applicable for bottle label, not applicable for outer carton)

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 10 mg (only applicable for outer carton, not applicable for bottle label)

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC (only applicable for outer carton, not applicable for bottle label)  
SN (only applicable for outer carton, not applicable for bottle label)  
NN (only applicable for outer carton, not applicable for bottle label)



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON FOR UNIT PACK FOR 15 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 15 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 film-coated tablets  
14 film-coated tablets  
28 film-coated tablets  
42 film-coated tablets  
98 film-coated tablets  
10 x 1 film-coated tablets  
100 x 1 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/011	14 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/012	28 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/013	42 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/014	98 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/015	10 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/016	100 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/038	10 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/048	14 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xarelto 15 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX) FOR 15 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 15 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 100 (10 packs of 10 x 1) film-coated tablets.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
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Bayer AG  
51368 Leverkusen  
Germany

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/08/472/023    100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
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<b>16. INFORMATION IN BRAILLE</b>
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Xarelto 15 mg

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) FOR 15 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 15 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 x 1 film-coated tablets.  
Component of a multipack, can't be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/023 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xarelto 15 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>UNIT DOSE BLISTER (10 X 1 TABLETS) FOR 15 MG</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 15 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 14 TABLETS FOR 15 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 15 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.



<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 10 TABLETS FOR 15 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 15 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
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Bayer (logo)

<b>3. EXPIRY DATE</b>
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EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 15 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 15 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/036      100 film-coated tablets      (HDPE Bottle)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription. (only applicable for bottle label, not applicable for outer carton)

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 15 mg (only applicable for outer carton, not applicable for bottle label)

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC (only applicable for outer carton, not applicable for bottle label)  
SN (only applicable for outer carton, not applicable for bottle label)  
NN (only applicable for outer carton, not applicable for bottle label)

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON FOR UNIT PACK FOR 20 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 20 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 film-coated tablets  
14 film-coated tablets  
28 film-coated tablets  
98 film-coated tablets  
10 x 1 film-coated tablets  
100 x 1 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/017	14 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/018	28 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/019	98 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/020	10 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/021	100 x 1 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/039	10 film-coated tablets	(PP/Aluminium foil blisters)
EU/1/08/472/049	14 film-coated tablets	(PVC/PVDC/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xarelto 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF MULTIPACK (INCLUDING BLUE BOX) FOR 20 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 20 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack: 100 (10 packs of 10 x 1) film-coated tablets.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/024 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) FOR 20 MG****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 20 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

10 x 1 film-coated tablets.  
Component of a multipack, can't be sold separately.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**



**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/024 100 film-coated tablets (10 x 10 x 1) (multipack) (PP/Aluminium foil blisters)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Xarelto 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>UNIT DOSE BLISTER (10 X 1 TABLETS) FOR 20 MG</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 20 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
-----------------

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
--

<b>BLISTER OF 14 TABLETS FOR 20 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 20 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Bayer (logo)

<b>3. EXPIRY DATE</b>
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EXP

<b>4. BATCH NUMBER</b>
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Lot

<b>5. OTHER</b>
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Mon.  
Tue.  
Wed.  
Thu.  
Fri.  
Sat.  
Sun.

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b>
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<b>BLISTER OF 10 TABLETS FOR 20 MG</b>
--

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

Xarelto 20 mg tablets  
rivaroxaban

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
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Bayer (logo)

<b>3. EXPIRY DATE</b>
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EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot

<b>5. OTHER</b>
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**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 20 MG**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 mg film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each film-coated tablet contains 20 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

100 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/037      100 film-coated tablets      (HDPE Bottle)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription. (only applicable for bottle label, not applicable for outer carton)

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 20 mg (only applicable for outer carton, not applicable for bottle label)

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC (only applicable for outer carton, not applicable for bottle label)  
SN (only applicable for outer carton, not applicable for bottle label)  
NN (only applicable for outer carton, not applicable for bottle label)

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****OUTER CARTON OF TREATMENT INITIATION PACK (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG) (INCLUDING BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg  
Xarelto 20 mg  
film-coated tablets  
rivaroxaban

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each red film-coated tablet for week 1, 2 and 3 contains 15 mg rivaroxaban.  
Each brown-red film-coated tablet for week 4 contains 20 mg rivaroxaban.

**3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Each pack of 49 film-coated tablets contains:  
42 film-coated tablets of 15 mg rivaroxaban  
7 film-coated tablets of 20 mg rivaroxaban

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

Treatment Initiation Pack

This treatment initiation pack is only for the first 4 weeks of treatment.

**DOSE**

Day 1 to 21: One 15 mg tablet twice a day (one 15 mg tablet in the morning and one in the evening) together with food.

From Day 22: One 20 mg tablet once a day (taken at same time each day) together with food.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS****10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/040      42 film-coated tablets of 15 mg rivaroxaban and  
7 film-coated tablets of 20 mg rivaroxaban  
(treatment initiation pack)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Xarelto 15 mg  
Xarelto 20 mg

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC  
SN  
NN



## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

### **WALLET OF TREATMENT INITIATION PACK (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG) (WITHOUT BLUE BOX)**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg  
Xarelto 20 mg  
film-coated tablets  
rivaroxaban

#### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each red film-coated tablet for week 1, 2 and 3 contains 15 mg rivaroxaban.  
Each brown-red film-coated tablet for week 4 contains 20 mg rivaroxaban.

#### **3. LIST OF EXCIPIENTS**

Contains lactose. See package leaflet for further information.

#### **4. PHARMACEUTICAL FORM AND CONTENTS**

Each pack of 49 film-coated tablets contains:  
42 film-coated tablets of 15 mg rivaroxaban  
7 film-coated tablets of 20 mg rivaroxaban

#### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
Oral use.

Treatment Initiation Pack

This treatment initiation pack is only for the first 4 weeks of treatment.

##### ***Back and front side***

##### **DOSE and DOSING SCHEME**

Day 1 to 21: One 15 mg tablet twice a day (one 15 mg tablet in the morning and one in the evening) with food.

From Day 22: One 20 mg tablet once a day (taken at same time each day) with food.

Initial treatment    Xarelto 15 mg twice a day    First 3 weeks  
Continuous treatment    Xarelto 20 mg once a day    Week 4 onwards    Visit your doctor to ensure continued treatment.  
To be taken with food.

Xarelto 15 mg  
Start of therapy  
15 mg  
twice a day  
Start date  
WEEK 1, WEEK 2, WEEK 3  
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

*sun as symbol*  
*moon as symbol*

Dose change  
Xarelto 20 mg  
20 mg  
once a day  
taken at same time each day  
Date of dose change  
WEEK 4  
DAY 22 DAY 23 DAY 24 DAY 25 DAY 26 DAY 27 DAY 28

<b>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</b>
--

Keep out of the sight and reach of children.

<b>7. OTHER SPECIAL WARNING(S), IF NECESSARY</b>
--

<b>8. EXPIRY DATE</b>
-----------------------

EXP

<b>9. SPECIAL STORAGE CONDITIONS</b>
--------------------------------------

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/040

42 film-coated tablets of 15 mg rivaroxaban and  
7 film-coated tablets of 20 mg rivaroxaban  
(treatment initiation pack)

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER OF TREATMENT INITIATION PACK IN WALLET (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg tablets

Xarelto 20 mg tablets

rivaroxaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Bayer (logo)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

## PARTICULARS TO APPEAR ON THE OUTER PACKAGING

### OUTER CARTON FOR GLASS BOTTLE 100 ML (GRANULES) (INCLUDING BLUE BOX)

#### 1. NAME OF THE MEDICINAL PRODUCT

Xarelto 1 mg/mL granules for oral suspension  
rivaroxaban  
For children weighing less than 4 kg

#### 2. STATEMENT OF ACTIVE SUBSTANCE(S)

The granules contain 19.69 mg rivaroxaban per gram.  
The glass bottle contains 51.7 mg rivaroxaban.  
Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

#### 3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See package leaflet for further information.

#### 4. PHARMACEUTICAL FORM AND CONTENTS

##### Granules for oral suspension

The bottle contains 2.625 g granules to be resuspended in 50 mL water.

1 bottle 100 mL  
1 water syringe 50 mL  
2 blue syringes 1 mL  
1 adapter

#### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please ask your pharmacist or doctor to fill in the prescription information:

Body weight of the child:        kg

Dose for the child:        mL

This dose is to be given to the child three times a day

**Shake after preparation at least 60 seconds.**

**Shake before each use at least 10 seconds.**



Oral use only after reconstitution.

Read the package leaflet and the Instructions for Use before use.

<b>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</b>
--

Keep out of the sight and reach of children.

<b>7. OTHER SPECIAL WARNING(S), IF NECESSARY</b>
--

<b>8. EXPIRY DATE</b>
-----------------------

EXP

After reconstitution the suspension is stable for 14 days.

<b>9. SPECIAL STORAGE CONDITIONS</b>
--------------------------------------

Do not store above 30 °C. Do not freeze. Store the prepared suspension upright.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Bayer AG  
51368 Leverkusen  
Germany

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/08/472/050

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
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Xarelto 1 mg/mL

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING****LABEL FOR GLASS BOTTLE 100 ML (GRANULES) (WITHOUT BLUE BOX)****1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 1 mg/mL granules for oral suspension  
rivaroxaban

For children weighing less than 4 kg.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

The granules contain 19.69 mg rivaroxaban per gram.  
The bottle contains 51.7 mg rivaroxaban.  
Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

**3. LIST OF EXCIPIENTS**

Contains sodium benzoate (E 211). See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Granules for oral suspension

2.625 g granules to be resuspended in 50 mL water.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

**Shake after preparation at least 60 seconds.**

**Shake before each use at least 10 seconds.**



Oral use only after reconstitution.

Read the package leaflet and the Instructions for Use before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.



**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

Expiry date (= date of preparation + 14 days):

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C. Do not freeze. Store the prepared suspension upright.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/050

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**OUTER CARTON FOR GLASS BOTTLE 250 ML (GRANULES) (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 1 mg/mL granules for oral suspension  
rivaroxaban  
For children weighing 4 kg and more.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

The granules contain 19.69 mg rivaroxaban per gram.  
The glass bottle contains 103.4 mg rivaroxaban.  
Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

**3. LIST OF EXCIPIENTS**

Contains sodium benzoate (E 211). See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

**Granules for oral suspension**

The bottle contains 5.25 g granules to be resuspended in 100 mL water.

1 bottle 250 mL  
1 water syringe 100 mL  
2 blue syringes 5 mL  
2 blue syringes 10 mL  
1 adapter

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Please ask your pharmacist or doctor to fill in the prescription information:

Body weight of the child:        kg

Dose for the child:        mL

This dose is to be given to the child (tick the box):

- ☐ Once daily  
☐ Twice daily  
☐ Three times a day

**Shake after preparation at least 60 seconds.**

**Shake before each use at least 10 seconds.**



Oral use only after reconstitution.

Read the package leaflet and the Instructions for Use before use.

<b>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</b>
--

Keep out of the sight and reach of children.

<b>7. OTHER SPECIAL WARNING(S), IF NECESSARY</b>
--

<b>8. EXPIRY DATE</b>
-----------------------

EXP

After reconstitution the suspension is stable for 14 days.

<b>9. SPECIAL STORAGE CONDITIONS</b>
--------------------------------------

Do not store above 30 °C. Do not freeze. Store the prepared suspension upright.

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Bayer AG  
51368 Leverkusen  
Germany

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/08/472/051

<b>13. BATCH NUMBER</b>
-------------------------

Batch

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

Xarelto 1 mg/mL

<b>17. UNIQUE IDENTIFIER – 2D BARCODE</b>
---

2D barcode carrying the unique identifier included.

<b>18. UNIQUE IDENTIFIER - HUMAN READABLE DATA</b>
--

PC  
SN  
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING**

**LABEL FOR GLASS BOTTLE 250 ML (GRANULES) (WITHOUT BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 1 mg/mL granules for oral suspension  
rivaroxaban

For children weighing 4 kg and more.

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

The granules contain 19.69 mg rivaroxaban per gram.  
The bottle contains 103.4 mg rivaroxaban.  
Following reconstitution the oral suspension contains 1 mg rivaroxaban per mL.

**3. LIST OF EXCIPIENTS**

Contains sodium benzoate (E 211). See package leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Granules for oral suspension  
5.25 g granules to be resuspended in 100 mL water.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

**Shake after preparation at least 60 seconds.**

**Shake before each use at least 10 seconds.**



Oral use only after reconstitution.

Read the package leaflet and the Instructions for Use before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

Expiry date (= date of preparation + 14 days):

EXP

**9. SPECIAL STORAGE CONDITIONS**

Do not store above 30 °C. Do not freeze. Store upright after reconstitution.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Bayer AG  
51368 Leverkusen  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/08/472/051

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PATIENT ALERT CARD****[Xarelto tablets 2.5 mg / 10 mg / 15 mg / 20 mg / treatment initiation pack]****Patient Alert Card**

Bayer (logo)

**Xarelto 2.5 mg** (tick box to tick the prescribed dose)**Xarelto 10 mg** (tick box to tick the prescribed dose)**Xarelto 15 mg** (tick box to tick the prescribed dose)**Xarelto 20 mg** (tick box to tick the prescribed dose)**♦ Keep this card with you at all times****♦ Present this card to every physician or dentist prior to treatment****I am under anticoagulation treatment with Xarelto (rivaroxaban)**

Name:

Address:

Birth date:

Weight:

Other medicines / conditions:

**In case of emergency, please notify:**

Doctor's name:

Doctor's phone:

Doctor's stamp:

**Please also notify:**

Name:

Phone:

Relationship:

**Information for health care providers:****♦ INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto.****What should I know about Xarelto?****♦ Xarelto thins the blood, which prevents you from getting dangerous blood clots.****♦ Xarelto must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, **never skip a dose.******♦ You must not stop taking Xarelto without first talking to your doctor as your risk of blood clots may increase.****♦ Tell your health care provider about any other medicines you are currently taking, took recently or intend to start taking, before you start Xarelto.****♦ Tell your health care provider that you are taking Xarelto before any surgery or invasive procedure.****When should I seek advice from my health care provider?**

When taking a blood thinner such as Xarelto it is important to be aware of its possible side effects.

Bleeding is the most common side effect. Do not start taking Xarelto if you know you are at risk of bleeding, without first discussing this with your doctor. Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:

**♦ pain****♦ swelling or discomfort****♦ headache, dizziness or weakness****♦ unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding****♦ menstrual flow or vaginal bleeding that is heavier than normal****♦ blood in your urine which may be pink or brown, red or black stools****♦ coughing up blood, or vomiting blood or material that looks like coffee grounds**

**How do I take Xarelto?**

- ◆ To ensure optimal protection, Xarelto
  - 2.5 mg can be taken with or without food
  - 10 mg can be taken with or without food
  - 15 mg must be taken with food
  - 20 mg must be taken with food



**PATIENT ALERT CARD****[Xarelto 1 mg/mL granules for oral suspension]****Patient Alert Card**

Bayer (logo)

**Xarelto 1 mg/mL granules for oral suspension****Information to caregivers/patients:**

- ◆ **Keep this card with you at all times.**
- ◆ **Present this card to every physician or dentist prior to treatment of the patient.**

[QR code], [web address]

Watch the educational video showing how to prepare and administer the oral suspension.

**The patient who is under anticoagulation treatment with Xarelto (rivaroxaban):**

Name:

Address:

Birth date:

Weight:

Other medicines / conditions:

**In case of emergency, please notify:**

Doctor's name:

Doctor's phone:

Doctor's stamp:

**Please also notify:**

Name:

Phone:

Relationship:

**Information for health care providers:**

- ◆ INR values should not be used as they are not a dependable measure of the anticoagulant activity of Xarelto.

**What should I know about Xarelto?**

- ◆ Xarelto thins the blood, which prevents from getting dangerous blood clots.
- ◆ Xarelto must be taken exactly as prescribed by the doctor. To ensure optimal protection from blood clots, **never skip a dose.**
- ◆ You must not stop giving/taking Xarelto without first talking to the doctor as the risk of blood clots may increase.
- ◆ Tell the health care provider about any other medicines the child is/you are currently taking, took recently or intend to start taking, before starting Xarelto.
- ◆ Tell the health care provider that the child is/you are taking Xarelto before any surgery or invasive procedure.

**When should I seek advice from a health care provider?**

When taking a blood thinner such as Xarelto it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start giving Xarelto to the child/taking Xarelto if you know the child is/you are at risk of bleeding, without first discussing this with the doctor. Tell the

health care provider straight away if the child has/you have any signs or symptoms of bleeding such as the following:

- ◆ pain
- ◆ swelling or discomfort
- ◆ headache, dizziness or weakness
- ◆ unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- ◆ menstrual flow or vaginal bleeding that is heavier than normal
- ◆ blood in the urine which may be pink or brown, red or black stools
- ◆ coughing up blood, or vomiting blood or material that looks like coffee grounds

**How do I give Xarelto to the child?/ How do I take Xarelto?**

◆ To ensure optimal protection, Xarelto 1 mg/mL must be given/taken with feeding (breast milk or formula feeding) or with a meal.

It can be administered through a nasogastric or gastric feeding tube.

## **B. PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Xarelto 2.5 mg film-coated tablets** rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xarelto is and what it is used for
2. What you need to know before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Contents of the pack and other information

#### **1. What Xarelto is and what it is used for**

You have been given Xarelto because

- you have been diagnosed with an acute coronary syndrome (a group of conditions that includes heart attack and unstable angina, a severe type of chest pain) and have been shown to have had an increase in certain cardiac blood tests.  
Xarelto reduces the risk in adults of having another heart attack or reduces the risk of dying from a disease related to your heart or your blood vessels.  
Xarelto will not be given to you on its own. Your doctor will also tell you to take either:
  - acetylsalicylic acid or
  - acetylsalicylic acid plus clopidogrel or ticlopidine.

or

- you have been diagnosed with a 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 blood clots (atherothrombotic events).  
Xarelto will not be given to you on its own. Your doctor will also tell you to take acetylsalicylic acid.  
In some cases, if you get Xarelto after a procedure to open a narrowed or closed artery of your leg to restore blood flow, your doctor may also prescribe clopidogrel for you to take in addition to acetylsalicylic acid for a short while.

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.

#### **2. What you need to know before you take Xarelto**

##### **Do not take Xarelto**

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)

- if you are bleeding excessively
- if you 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 you 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 you have an acute coronary syndrome and previously had a bleeding or a blood clot in your brain (stroke)
- if you have coronary artery disease or peripheral artery disease and previously had a bleeding in your brain (stroke) or where there was a blockage of the small arteries providing blood to the brain's deep tissues (lacunar stroke) or if you had a blood clot in your brain (ischaemic, non-lacunar stroke) in the previous month
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

**Do not take Xarelto and tell your doctor** if any of these apply to you.

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Xarelto.

Xarelto should not be used in combination with certain other medicines which reduce blood clotting such as prasugrel or ticagrelor other than acetylsalicylic acid and clopidogrel/ticlopidine.

### **Take special care with Xarelto**

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you 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 (see section “Other medicines and Xarelto”)
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your 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) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
  - you are older than 75 years
  - you weigh less than 60 kg
  - you have a coronary artery disease with severe symptomatic heart failure
- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

**If any of the above apply to you, tell your doctor** before you take Xarelto. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

### **If you need to have an operation**

- it is very important to take Xarelto before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your 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 you have been told by your doctor

- tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

### **Children and adolescents**

Xarelto 2.5 mg tablets are **not recommended for people under 18 years of age**. There is not enough information on their use in children and adolescents.

### **Other medicines and Xarelto**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- If you are taking
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
  - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
  - 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, prasugrel and ticagrelor (see section "Warnings and Precautions"))
  - 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))

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- If you are taking
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be reduced. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

### **Pregnancy and breast-feeding**

Do not take Xarelto if you are pregnant or breast-feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Xarelto. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

### **Driving and using machines**

Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, "Possible side effects"). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

### **Xarelto contains lactose and sodium**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

### **3. How to take Xarelto**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

#### **How much to take**

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). This medicine can be taken with or without food.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Xarelto. The tablet may be crushed and mixed with water or apple puree immediately before you take it.

If necessary, your doctor may also give you the crushed Xarelto tablet through a stomach tube.

Xarelto will not be given to you on its own.

Your doctor will also tell you to take acetylsalicylic acid.

If you get Xarelto after an acute coronary syndrome, your doctor may tell you to also take clopidogrel or ticlopidine.

If you get Xarelto after a procedure to open a narrowed or closed artery of your leg to restore blood flow, your doctor may also prescribe clopidogrel for you to take in addition to acetylsalicylic acid for a short while.

Your doctor will tell you how much of these to take (usually between 75 to 100 mg acetylsalicylic acid daily or a daily dose of 75 to 100 mg acetylsalicylic acid plus a daily dose of either 75 mg clopidogrel or a standard daily dose of ticlopidine).

#### **When to start Xarelto**

Treatment with Xarelto after an acute coronary syndrome should be started as soon as possible after stabilisation of the acute coronary syndrome, at the earliest 24 hours after admission to hospital and at the time when parenteral (via injection) anticoagulation therapy would normally be stopped.

Your doctor will tell you when to start treatment with Xarelto if you have been diagnosed with coronary artery disease or peripheral artery disease.

Your doctor will decide how long you must continue treatment.

#### **If you take more Xarelto than you should**

Contact your doctor immediately if you have taken too many Xarelto tablets. Taking too much Xarelto increases the risk of bleeding.

#### **If you forget to take Xarelto**

Do not take a double dose to make up for a missed dose. If you miss a dose, take your next dose at the usual time.

#### **If you stop taking Xarelto**

Take Xarelto on a regular basis and for as long as your doctor keeps prescribing it.

Do not stop taking Xarelto without talking to your doctor first. If you stop taking this medicine, it may increase your risk of having another heart attack or stroke or dying from a disease related to your heart or your blood vessels.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### **4. Possible side effects**

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Xarelto may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Tell your doctor immediately if you experience any of the following side effects:**

- **Signs of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
  - long or excessive bleeding
  - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectorisYour doctor may decide to keep you under closer observation or change the treatment.
- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).The frequency of these side effects is very rare (up to 1 in 10,000 people).
- **Signs of severe allergic reactions**
  - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

**Overall list of possible 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
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- 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
- 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 (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)



- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

**Rare** (may affect up to 1 in 1,000 people)

- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

### Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Xarelto

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

### Crushed tablets

Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Xarelto contains

- The active substance is rivaroxaban. Each tablet contains 2.5 mg of rivaroxaban.
- The other ingredients are:  
Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose (2910), sodium laurilsulfate, magnesium stearate. See section 2 “Xarelto contains lactose and sodium”.  
Tablet film coat: macrogol (3350), hypromellose (2910), titanium dioxide (E 171), iron oxide yellow (E 172).

**What Xarelto looks like and contents of the pack**

Xarelto 2.5 mg film-coated tablets are light yellow, round, biconvex and marked with the BAYER-cross on one side and “2.5” and a triangle on the other side.

They come

- in blisters in cartons of 14, 20, 28, 30, 56, 60, 98, 168 or 196 film-coated tablets or
- in unit dose blisters in cartons of 10 x 1 or 100 x 1 or
- in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets or
- in bottles of 100 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**

Bayer AG  
51368 Leverkusen  
Germany

**Manufacturer**

The manufacturer can be identified by the batch number printed on the side flap of the carton and on each blister or bottle:

- If the first and second characters are BX, the manufacturer is  
Bayer AG  
Kaiser-Wilhelm-Allee  
51368 Leverkusen  
Germany
- If the first and second characters are IT, the manufacturer is  
Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy
- If the first and second characters are BT, the manufacturer is  
Bayer Bitterfeld GmbH  
Ortsteil Greppin, Salegaster Chaussee 1  
06803 Bitterfeld-Wolfen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

## **Package leaflet: Information for the user**

### **Xarelto 10 mg film-coated tablets** rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xarelto is and what it is used for
2. What you need to know before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Contents of the pack and other information

#### **1. What Xarelto is and what it is used for**

Xarelto contains the active substance rivaroxaban and is used in adults to

- prevent blood clots in the veins after a hip or knee replacement operation. Your doctor has prescribed this medicine for you because after an operation you are at an increased risk of getting blood clots.
- 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.

#### **2. What you need to know before you take Xarelto**

##### **Do not take Xarelto**

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you 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 you 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 you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

**Do not take Xarelto and tell your doctor** if any of these apply to you.

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Xarelto.

### **Take special care with Xarelto**

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - moderate or severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you 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 (see section “Other medicines and Xarelto”)
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your 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) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.

**If any of the above apply to you, tell your doctor** before you take Xarelto. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

### **If you need to have an operation**

- it is very important to take Xarelto before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Xarelto exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

### **Children and adolescents**

Xarelto 10 mg tablets are **not recommended for people under 18 years of age**. There is not enough information on their use in children and adolescents.

### **Other medicines and Xarelto**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- If you are taking
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
  - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
  - 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))

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- - If you are taking
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be reduced. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

### **Pregnancy and breast-feeding**

Do not take Xarelto if you are pregnant or breast-feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Xarelto. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

### **Driving and using machines**

Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4 "Possible side effects"). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

### **Xarelto contains lactose and sodium**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

## **3. How to take Xarelto**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

### **How much to take**

- 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 your legs and blood clots in the blood vessels of your 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. Your doctor has prescribed you Xarelto 10 mg once a day.

Swallow the tablet preferably with water.  
Xarelto can be taken with or without food.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Xarelto. The tablet may be crushed and mixed with water or apple puree immediately before you take it.

If necessary, your doctor may also give you the crushed Xarelto tablet through a stomach tube.

### **When to take Xarelto**

Take the tablet every day until your doctor tells you to stop.

Try to take the tablet at the same time every day to help you to remember it.

Your doctor will decide how long you must continue treatment.

To prevent blood clots in the veins after a hip or knee replacement operation:

Take the first tablet 6 - 10 hours after your operation.

If you have had a major hip operation you will usually take the tablets for 5 weeks.

If you have had a major knee operation you will usually take the tablets for 2 weeks.

### **If you take more Xarelto than you should**

Contact your doctor immediately if you have taken too many Xarelto tablets. Taking too much Xarelto increases the risk of bleeding.

### **If you forget to take Xarelto**

If you have missed a dose, take it as soon as you remember. Take the next tablet on the following day and then carry on taking a tablet once a day as normal.

Do not take a double dose to make up for a forgotten tablet.

### **If you stop taking Xarelto**

Do not stop taking Xarelto without talking to your doctor first, because Xarelto prevents the development of a serious condition.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## **4. Possible side effects**

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Xarelto may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

### **Tell your doctor immediately if you experience any of the following side effects:**

- **Signs of bleeding**
    - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
    - long or excessive bleeding
    - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris
- Your doctor may decide to keep you under closer observation or change the treatment.



- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Signs of severe allergic reactions**
    - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.
- The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

### **Overall list of possible 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
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- 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
- 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 (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

#### **Rare** (may affect up to 1 in 1,000 people)

- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via **the national reporting system** listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Xarelto**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

### Crushed tablets

Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Xarelto contains**

- 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 (2910), sodium laurilsulfate, magnesium stearate. See section 2 “Xarelto contains lactose and sodium”.  
Tablet film coat: macrogol (3350), hypromellose (2910), titanium dioxide (E 171), iron oxide red (E 172).

### **What Xarelto looks like and contents of the pack**

Xarelto 10 mg film-coated tablets are light red, round, biconvex and marked with the BAYER-cross on one side and “10” and a triangle on the other side.

They come

- in blisters in cartons of 5, 10, 14, 28, 30 or 98 film-coated tablets or
- in unit dose blisters in cartons of 10 x 1 or 100 x 1 or
- in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets or
- in bottles of 100 film-coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Bayer AG  
51368 Leverkusen  
Germany

## **Manufacturer**

The manufacturer can be identified by the batch number printed on the side flap of the carton and on each blister or bottle:

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20024 Garbagnate Milanese  
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Bayer Bitterfeld GmbH  
Ortsteil Greppin, Salegaster Chaussee 1  
06803 Bitterfeld-Wolfen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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**Malta**

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**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

## **Package leaflet: Information for the user**

**Xarelto 15 mg film-coated tablets**

**Xarelto 20 mg film-coated tablets**

rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Xarelto is and what it is used for
2. What you need to know before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Contents of the pack and other information

### **1. What Xarelto is and what it is used for**

Xarelto contains the active substance rivaroxaban.

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.
- 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 is used in children and adolescents below 18 years and with a body weight of 30 kg or more to:

- treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs, following initial treatment of at least 5 days with injectable medicines used to treat blood clots.

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.

## **2. What you need to know before you take Xarelto**

### **Do not take Xarelto**

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you 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 you 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 you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or are breast-feeding

**Do not take Xarelto and tell your doctor** if any of these apply to you.

### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Xarelto.

### **Take special care with Xarelto**

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease for adults, and moderate or severe kidney disease for children and adolescents, since your kidney function may affect the amount of medicine that works in your body
  - if you 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 (see section “Other medicines and Xarelto”)
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your 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) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned

**If any of the above apply to you, tell your doctor** before you take Xarelto. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

### **If you need to have an operation**

- it is very important to take Xarelto before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your 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 you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

### Children and adolescents

Xarelto tablets are **not recommended for children with a body weight below 30 kg**.

There is not enough information on the use of Xarelto in children and adolescents in the adult indications.

### Other medicines and Xarelto

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- If you are taking
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
  - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
  - 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))

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- If you are taking
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be reduced. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

### Pregnancy and breast-feeding

Do not take Xarelto if you are pregnant or breast-feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Xarelto. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

### Driving and using machines

Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, "Possible side effects"). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

### Xarelto contains lactose and sodium

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".



### 3. How to take Xarelto

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You must take Xarelto together with a meal.  
Swallow the tablet(s) preferably with water.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Xarelto. The tablet may be crushed and mixed with water or apple puree immediately before you take it. This mixture should be immediately followed by food.

If necessary, your doctor may also give you the crushed Xarelto tablet through a stomach tube.

#### How much to take

- **Adults**

- To prevent blood clots in brain (stroke) and other blood vessels in your body  
The recommended dose is one tablet Xarelto 20 mg once a day.  
If you have kidney problems, the dose may be reduced to one tablet Xarelto 15 mg once a day.

If you need a procedure to treat blocked blood vessels in your 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 your kidneys are not working properly) in addition to an antiplatelet medicine such as clopidogrel.

- To treat blood clots in the veins of your legs and blood clots in the blood vessels of your 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 your doctor may decide to continue treatment with either one 10 mg tablet once a day or one 20 mg tablet once a day.  
If you have kidney problems and take one tablet Xarelto 20 mg once a day, your 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.

- **Children and adolescents**

The dose of Xarelto depends on the body weight, and will be calculated by the doctor.

- The recommended dose for children and adolescents with a **body weight between 30 kg and less than 50 kg** is one **Xarelto 15 mg tablet** once a day.
- The recommended dose for children and adolescents with a **body weight of 50 kg or more** is one **Xarelto 20 mg tablet** once a day.

Take each Xarelto dose with a drink (e.g. water or juice) during a meal. Take the tablets every day at approximately the same time. Consider setting an alarm to remind you.

For parents or caregivers: please observe the child to ensure the full dose is taken.

As the Xarelto dose is based on body weight it is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes.

**Never adjust the dose of Xarelto by yourself.** The doctor will adjust the dose if necessary.

Do not split the tablet in an attempt to provide a fraction of a tablet dose. If a lower dose is required please use the alternative presentation of Xarelto granules for oral suspension.

For children and adolescents who are unable to swallow tablets whole, please use Xarelto granules for oral suspension.

If the oral suspension is not available, you may crush the Xarelto tablet and mix with water or apple puree immediately before taking. Take some food after taking this mixture. If necessary, your doctor may also give the crushed Xarelto tablet through a stomach tube.

**If you spit up the dose or vomit**

- less than 30 minutes after you have taken Xarelto, take a new dose.
- more than 30 minutes after you have taken Xarelto, **do not** take a new dose. In this case, take the next Xarelto dose at the usual time.

Contact the doctor if you repeatedly spit up the dose or vomit after taking Xarelto.

**When to take Xarelto**

Take the tablet(s) every day until your doctor tells you to stop.

Try to take the tablet(s) at the same time every day to help you to remember it.

Your doctor will decide how long you must continue treatment.

To prevent blood clots in the brain (stroke) and other blood vessels in your body:

If your heart beat needs to be restored to normal by a procedure called cardioversion, take Xarelto at the times your doctor tells you.

**If you forget to take Xarelto**

- Adults, children and adolescents:

If you are taking one 20 mg tablet or one 15 mg tablet **once** a day and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

- Adults:

If you are taking one 15 mg tablet **twice** a day and have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets in a single day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.

**If you take more Xarelto than you should**

Contact your doctor immediately if you have taken too many Xarelto tablets. Taking too much Xarelto increases the risk of bleeding.

**If you stop taking Xarelto**

Do not stop taking Xarelto without talking to your doctor first, because Xarelto treats and prevents serious conditions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Xarelto may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Tell your doctor immediately if you or the child experience any of the following side effects:**

- **Signs of bleeding**

- bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you under closer observation or change the treatment.

- **Signs of severe skin reactions**

- spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
- a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Signs of severe allergic reactions**

- swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

**Overall list of possible side effects found in adults, children and adolescents**

**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
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- 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
- 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 (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

**Rare** (may affect up to 1 in 1,000 people)

- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

**Side effects in children and adolescents**

In general, the side effects observed in children and adolescents treated with Xarelto were similar in type to those observed in adults and were primarily mild to moderate in severity.

Side effects that were observed more often in children and adolescents:

**Very common** (may affect more than 1 in 10 people)

- headache
- fever
- nose bleeding
- vomiting

**Common** (may affect up to 1 in 10 people)

- raised heartbeat
- blood tests may show an increase in bilirubin (bile pigment)
- thrombocytopenia (low number of platelets which are cells that help blood to clot)
- heavy menstrual bleeding

**Uncommon** (may affect up to 1 in 100 people)

- blood tests may show an increase in a subcategory of bilirubin (direct bilirubin, bile pigment)

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Xarelto**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister or bottle after EXP.

The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

#### Crushed tablets

Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Xarelto contains**

- 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 (2910), sodium laurilsulfate, magnesium stearate. See section 2 “Xarelto contains lactose and sodium”  
Tablet film coat: macrogol (3350), hypromellose (2910), titanium dioxide (E 171), iron oxide red (E 172).

### **What Xarelto looks like and contents of the pack**

Xarelto 15 mg film-coated tablets are red, round, biconvex and marked with the BAYER-cross on one side and “15” and a triangle on the other side.

They come

- in blisters in cartons of 10, 14, 28, 42 or 98 film-coated tablets or
- in unit dose blisters in cartons of 10 x 1 or 100 x 1 or
- in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets or
- in bottles of 100 film-coated tablets.

Xarelto 20 mg film-coated tablets are brown-red, round, biconvex and marked with the BAYER-cross on one side and “20” and a triangle on the other.

They come

- in blisters in cartons of 10, 14, 28 or 98 film-coated tablets or
- in unit dose blisters in cartons of 10 x 1 or 100 x 1 or
- in multipacks comprising 10 cartons, each containing 10 x 1 film-coated tablets or
- in bottles of 100 film-coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Bayer AG  
51368 Leverkusen  
Germany

## **Manufacturer**

The manufacturer can be identified by the batch number printed on the side flap of the carton and on each blister or bottle:

- If the first and second characters are BX, the manufacturer is  
Bayer AG  
Kaiser-Wilhelm-Allee  
51368 Leverkusen  
Germany
- If the first and second characters are IT, the manufacturer is  
Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy
- If the first and second characters are BT, the manufacturer is  
Bayer Bitterfeld GmbH  
Ortsteil Greppin, Salegaster Chaussee 1  
06803 Bitterfeld-Wolfen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**United Kingdom (Northern Ireland)**  
Bayer AG  
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**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.



## **Package leaflet: Information for the user**

**Xarelto 15 mg film-coated tablets**

**Xarelto 20 mg film-coated tablets**

### **Treatment Initiation Pack**

Not for use in children.

rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

### **What is in this leaflet**

1. What Xarelto is and what it is used for
2. What you need to know before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Contents of the pack and other information

#### **1. What Xarelto is and what it is used for**

Xarelto contains the active substance rivaroxaban and is used in adults 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.

#### **2. What you need to know before you take Xarelto**

##### **Do not take Xarelto**

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you 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 you 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 you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

**Do not take Xarelto and tell your doctor** if any of these apply to you.

##### **Warnings and precautions**

Talk to your doctor or pharmacist before taking Xarelto.

### **Take special care with Xarelto**

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you 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 (see section “Other medicines and Xarelto”)
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your 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) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned

**If any of the above apply to you, tell your doctor** before you take Xarelto. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

### **If you need to have an operation**

- it is very important to take Xarelto before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your 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 you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

### **Children and adolescents**

Xarelto treatment initiation pack is **not recommended for people under 18 years of age** as it is specifically designed for initiation of treatment in adult patients and is not appropriate for use in children and adolescents.

### **Other medicines and Xarelto**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- If you are taking
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
  - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
  - 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))

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- If you are taking
  - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

**If any of the above apply to you, tell your doctor** before taking Xarelto, because the effect of Xarelto may be reduced. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

### **Pregnancy and breast-feeding**

Do not take Xarelto if you are pregnant or breast-feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Xarelto. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

### **Driving and using machines**

Xarelto may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, "Possible side effects"). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

### **Xarelto contains lactose and sodium**

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

## **3. How to take Xarelto**

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You must take Xarelto together with a meal.  
Swallow the tablet(s) preferably with water.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Xarelto. The tablet may be crushed and mixed with water or apple puree immediately before you take it. This mixture should be immediately followed by food.

If necessary, your doctor may also give you the crushed Xarelto tablet through a stomach tube.

**How much to take**

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.

This Xarelto 15 mg and 20 mg treatment initiation pack is only for the first 4 weeks of treatment.

Upon completion of this pack, treatment will continue on Xarelto 20 mg once daily as your doctor has told you.

If you have kidney problems, your 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.

**When to take Xarelto**

Take the tablet(s) every day until your doctor tells you to stop.

Try to take the tablet(s) at the same time every day to help you to remember it.

Your doctor will decide how long you must continue treatment.

**If you take more Xarelto than you should**

Contact your doctor immediately if you have taken too many Xarelto tablets. Taking too much Xarelto increases the risk of bleeding.

**If you forget to take Xarelto**

- If you are taking one 15 mg tablet twice a day and have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets in a single day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.
- If you are taking one 20 mg tablet once a day and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

**If you stop taking Xarelto**

Do not stop taking Xarelto without talking to your doctor first, because Xarelto treats and prevents serious conditions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. Possible side effects**

Like all medicines, Xarelto can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Xarelto may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Tell your doctor immediately if you experience any of the following side effects:**

- **Signs of bleeding**
    - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
    - long or excessive bleeding
    - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris
- Your doctor may decide to keep you under closer observation or change the treatment.

- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to 1 in 10,000 people).
- **Signs of severe allergic reactions**
  - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

### **Overall list of possible 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
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- 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
- 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 (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

#### **Rare** (may affect up to 1 in 1,000 people)

- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling

- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

### **Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Xarelto**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each wallet after EXP.

The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

### Crushed tablets

Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## **6. Contents of the pack and other information**

### **What Xarelto contains**

- The active substance is rivaroxaban. Each tablet contains 15 mg or 20 mg of rivaroxaban, respectively.
- The other ingredients are:  
Tablet core: microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, hypromellose (2910), sodium laurilsulfate, magnesium stearate. See section 2 “Xarelto contains lactose and sodium”. Tablet film coat: macrogol (3350), hypromellose (2910), titanium dioxide (E 171), iron oxide red (E 172).

### **What Xarelto looks like and contents of the pack**

Xarelto 15 mg film-coated tablets are red, round, biconvex and marked with the BAYER-cross on one side and “15” and a triangle on the other side.

Xarelto 20 mg film-coated tablets are brown-red, round, biconvex and marked with the BAYER-cross on one side and “20” and a triangle on the other.

First 4 weeks treatment initiation pack: each pack of 49 film-coated tablets for the first 4 weeks of treatment contains:

42 film-coated tablets of 15 mg rivaroxaban and 7 film-coated tablets of 20 mg rivaroxaban in a wallet.

## **Marketing Authorisation Holder**

Bayer AG  
51368 Leverkusen  
Germany

## **Manufacturer**

The manufacturer can be identified by the batch number printed on the side flap of the carton and on each blister or bottle:

- If the first and second characters are BX, the manufacturer is  
Bayer AG  
Kaiser-Wilhelm-Allee  
51368 Leverkusen  
Germany
- If the first and second characters are IT, the manufacturer is  
Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy
- If the first and second characters are BT, the manufacturer is  
Bayer Bitterfeld GmbH  
Ortsteil Greppin, Salegaster Chaussee 1  
06803 Bitterfeld-Wolfen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België / Belgique / Belgien**

Bayer SA-NV  
Tél/Tel: +32-(0)2-535 63 11

**България**

Байер България ЕООД  
Тел: +359-(0)2-424 72 80

**Česká republika**

Bayer s.r.o.  
Tel: +420-266 101 111

**Danmark**

Bayer A/S  
Tlf: +45-45 235 000

**Deutschland**

Bayer Vital GmbH  
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**Eesti**

Bayer OÜ  
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**Ελλάδα**

Bayer Ελλάς ABEE  
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**España**

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**France**

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**Hrvatska**

Bayer d.o.o.  
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**Ísland**

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**Lietuva**

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**Nederland**

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**Norge**

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Tlf: +47-23 13 05 00

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**Polska**

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**Portugal**

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**Slovenská republika**

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Tel: +421-(0)2-59 21 31 11

**Suomi/Finland**

Bayer Oy  
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**Sverige**  
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**Latvija**  
SIA Bayer  
Tel: +371-67 84 55 63

**United Kingdom (Northern Ireland)**  
Bayer AG  
Tel: +44-(0) 118 206 3000

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

## **Package leaflet: Information for the user**

### **Xarelto 1 mg/mL granules for oral suspension** rivaroxaban

**Read all of this leaflet carefully before you start taking this medicine because it contains important information. This leaflet has been written for the patient (“you”) and the parent or caregiver who will give this medicine to the child.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or the child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same.
- If you or the child get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet**

1. What Xarelto is and what it is used for
2. What you need to know before you take or give Xarelto
3. How to take or give Xarelto
4. Possible side effects
5. How to store Xarelto
6. Contents of the pack and other information

#### **1. What Xarelto is and what it is used for**

Xarelto contains the active substance rivaroxaban.

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.

Xarelto is used in full-term newborn babies, infants and toddlers, children and adolescents below 18 years to:

- treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs, following an initial treatment of at least 5 days with injectable medicines used to treat blood clots.

Read and follow the Instructions for Use provided with this medicine because it will show you how to prepare and take or give Xarelto oral suspension.

#### **2. What you need to know before you take or give Xarelto**

##### **Do not take or give Xarelto if you or the child**

- are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- are bleeding excessively
- 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)
- are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except
  - when changing medicines to prevent blood clotting or
  - while getting heparin through a venous or arterial line to keep it open.
- have a liver disease associated with an increased risk of bleeding
- are pregnant or breast-feeding

**Do not take or give Xarelto and tell your doctor if any of these apply to you or the child.**

## Warnings and precautions

Talk to your doctor or pharmacist before using Xarelto if:

- you or the child have an increased risk of bleeding. This could be the case in situations such as:
  - moderate or severe kidney disease; as the kidney function may affect the amount of medicine that works in the body
  - if you or the child are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), if these are absolutely necessary (see section “Do not take or give Xarelto”)
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the food pipe due to a disease where stomach acid goes upwards into the food pipe or tumours located in the stomach or bowels or genital tract or urinary tract
  - 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
- you or the child have a prosthetic heart valve
- you or the child have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots)
- your or the child’s blood pressure is unstable
- another treatment or surgical procedure is planned to remove the blood clot from the lungs

If any of the above apply to you or to the child, **tell your doctor** before you take or give Xarelto. The doctor will decide, if you or the child should be treated with this medicine and should be kept under closer observation.

**Do not give** Xarelto to children under 6 months of age who

- were born before 37 weeks of pregnancy, or
- weigh less than 2.6 kg, or
- had less than 10 days of breast or formula feeding

In these cases, dosing of Xarelto cannot be reliably determined and has not been studied in these children.

## If you or the child need to have an operation

- It is very important to take or give Xarelto before and after the operation exactly at the times your doctor has told you.
- If the operation involves a catheter or injection into the spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take or give Xarelto before and after the injection or removal of the catheter exactly at the times your doctor has told you
  - tell your doctor immediately if you or the child get numbness or weakness of the legs or problems with the bowel or bladder after the end of anaesthesia. In this case, urgent care is necessary.

## Children and adolescents

Xarelto oral suspension is to be used for patients below 18 years to treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs. There is not enough information on its use in children and adolescents in other indications.

## Other medicines and Xarelto

Tell your doctor or pharmacist if you or the child are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

- If you or the child are taking:
  - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
  - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
  - some 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)
  - medicines to relieve inflammation and pain (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))

If any of the above apply to you or the child, **tell your doctor** before taking or giving Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you or the child should be treated with this medicine and should be kept under closer observation. If the doctor thinks that you or the child are at increased risk of developing stomach or bowel ulcers, a preventive ulcer treatment might be necessary.

- If you or the child are taking:
  - some medicines to treat epilepsy (phenytoin, carbamazepine, phenobarbital)
  - St John's Wort (*Hypericum perforatum*), a herbal product used for depression
  - rifampicin, an antibiotic

If any of the above apply to you or the child, **tell your doctor** before taking or giving Xarelto, because the effect of Xarelto may be reduced. The doctor will decide, if you or the child should be treated with Xarelto and should be kept under closer observation.

### **Pregnancy and breast-feeding**

- If you or the adolescent are pregnant or breast-feeding **do not take or give Xarelto**.
- If there is a **chance** that you or the adolescent could **become pregnant**, a reliable **contraceptive** should be used while taking Xarelto.
- If you or the adolescent become pregnant while taking this medicine, tell your doctor immediately, who will decide how the treatment should be continued.

### **Driving and using machines**

Xarelto may cause dizziness or fainting. You or the child should not drive, ride a bicycle or use any tools or machines if affected by these symptoms.

### **Xarelto contains sodium benzoate and sodium**

This medicine contains 1.8 mg sodium benzoate (E 211) in each mL oral suspension. Sodium benzoate (E 211) may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old). This medicine contains less than 1 mmol sodium (23 mg) per millilitre, that is to say essentially "sodium-free".

## **3. How to take or give Xarelto**

Always take this medicine or give this medicine to the child exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Make sure that the correct information on how much and how often to take or give Xarelto is written on the designated area of the carton. If not, ask your pharmacist or doctor to provide the relevant information.

### **Instructions for Use**

For how to prepare and take or give the Xarelto oral suspension:

- See the Instructions for Use booklet included in the carton and
- Watch the educational video which you can access via the QR code which is displayed on the Patient Alert Card that is provided with this medicine.

### **How to take or give**

Take or give Xarelto oral suspension with feeding (breast milk or formula feeding) or with a meal. Each Xarelto dose has to be swallowed along with one typical serving of liquid (for example 20 mL in children aged 6 months up to 240 mL in adolescents). This typical serving may include usual amount of drink used for feeding (e.g. breast milk, infant formula, nutrition drink).

Your doctor may give the oral suspension also via a stomach tube.

### **How much to take or give**

The dose of Xarelto depends on the patient's body weight. It will be calculated by the doctor as an amount (volume) in millilitres (mL) of the oral suspension. This should be measured out using the blue syringe (either 1 mL or 5 mL or 10 mL syringe, see table 1) supplied with this medicine. Your doctor will prescribe the volume required including the particular syringe you should use.

Your doctor will tell you how much of the oral suspension you or the child must take.

Below is the table that your doctor will use. **Do not adjust the dose yourself.**

All materials to prepare and administer the oral suspension are provided with the medicine (except for drinking water.) Only use non-carbonated water to avoid bubbles. **Only use the syringe provided** to administer Xarelto to ensure accurate dosing. Do not use any other method to administer the solution, e.g. alternative syringe, spoon etc.

As the Xarelto dose is based on body weight it is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes, especially for children below 12 kg. This ensures that the child receives the correct dose of Xarelto.

**Table 1: Recommended dose for Xarelto in children**

Body weight [kg]	Single dose*	Daily frequency of intake	Total daily dose*	Suitable blue syringe
2.6 to under 3	0.8 mL	3 times	2.4 mL	1 mL
3 to under 4	0.9 mL		2.7 mL	
4 to under 5	1.4 mL		4.2 mL	5 mL
5 to under 7	1.6 mL		4.8 mL	
7 to under 8	1.8 mL		5.4 mL	
8 to under 9	2.4 mL		7.2 mL	
9 to under 10	2.8 mL		8.4 mL	
10 to under 12	3.0 mL		9.0 mL	
12 to under 30	5.0 mL	2 times	10.0 mL	5 mL or 10 mL
30 to under 50	15.0 mL	once	15.0 mL	10 mL
50 or more	20.0 mL		20.0 mL	
* 1 mL of the oral suspension corresponds to 1 mg rivaroxaban.				

Your doctor may also prescribe tablets if you or the child are able to swallow the tablet and are weighing at least 30 kg.

### **When to take or give Xarelto**

Take or give the oral suspension as directed every day until the doctor tells you to stop.

Take or give the oral suspension at the same time every day to help you to remember it. Consider setting an alarm to remind you.

Please observe the child to ensure the full dose is taken.

If the doctor has told you to take or give Xarelto:

- once a day, do this approximately 24 hours apart
- twice a day, do this approximately 12 hours apart
- three times a day, do this approximately 8 hours apart

Your doctor will decide how long you or the child must continue treatment.

**If you or the child spits up the dose or vomits**

- less than 30 minutes after the intake of Xarelto, take or give a new dose.
- more than 30 minutes after the intake of Xarelto, **do not** take or give a new dose. Continue to take or give the next Xarelto dose at the next scheduled time.

Contact the doctor if you or the child repeatedly spit up the dose or vomit after taking Xarelto.

**If you forget to take or give Xarelto**

- **If you are taking or giving Xarelto once a day**, take or give the missed Xarelto dose as soon as you remember on the same day. If this is not possible, skip this dose. Then take or give the next Xarelto dose on the following day. Do not take or give more than one dose per day.
- **If you are taking or giving Xarelto twice a day:**
  - Missed morning dose: Take or give the missed dose as soon as you remember. You may take or give it together with the evening dose.
  - Missed evening dose: You may take or give the missed dose only in the same evening. Do not take or give two doses the next morning.
- **If you are taking or giving Xarelto three times a day**, do not make up for the missed dose. Continue with the next scheduled dose (given every 8 hours).

On the day following a missed dose, continue as prescribed by the doctor once, twice or three times a day.

**If you take or give more Xarelto than you should**

Contact your doctor immediately if you have taken or given too much Xarelto oral suspension. Taking or giving too much Xarelto increases the risk of bleeding.

**If you stop taking or giving Xarelto**

Do not stop Xarelto without talking to your doctor first, because Xarelto treats and prevents serious conditions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

#### **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Xarelto may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

**Tell your doctor immediately if you or the child experience any of the following side effects:**

- **Signs of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
  - long or excessive bleeding
  - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you or the child under closer observation or change the treatment.

- **Signs of severe skin reactions**

- spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis)
- a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome)

The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Signs of severe allergic reactions**

- swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

**Overall list of possible side effects found in adults and children and adolescents:**

**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
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- 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
- 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 (see above, possible side effects which may be a sign of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

**Rare** (may affect up to 1 in 1,000 people)

- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

**Not known** (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

### **Side effects in children and adolescents**

In general, the side effects observed in children and adolescents treated with Xarelto were similar in type to those observed in adults and were primarily mild to moderate in severity.

Side effects that were observed more often in children and adolescents:

**Very common** (may affect more than 1 in 10 people)

- Headache
- fever
- nose bleeding
- vomiting

**Common** (may affect up to 1 in 10 people)

- raised heartbeat
- blood tests may show an increase in bilirubin (bile pigment)
- thrombocytopenia (low number of platelets which are cells that help blood to clot)
- heavy menstrual bleeding

**Uncommon** (may affect up to 1 in 100 people)

- blood tests may show an increase in a subcategory of bilirubin (direct bilirubin, bile pigment)

### **Reporting of side effects**

If you or the child get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

## **5. How to store Xarelto**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on the bottle after EXP.

The expiry date refers to the last day of that month.

After preparation, the shelf life of the suspension is 14 days at room temperature.

Do not store above 30 °C.

Do not freeze. Store the prepared suspension upright.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.



## 6. Contents of the pack and other information

### What Xarelto contains

- The active substance is rivaroxaban. One glass bottle contains 51.7 mg (for the 100 mL bottle) or 103.4 mg (for the 250 mL bottle) of rivaroxaban. After preparation, each mL of the suspension contains 1 mg of rivaroxaban.
- The other ingredients are:  
Citric acid, anhydrous (E 330), hypromellose (2910), mannitol (E 421), microcrystalline cellulose, carboxymethylcellulose sodium, sodium benzoate (E 211) (see section 2 “Xarelto contains sodium benzoate and sodium”), sucralose (E 955), xanthan gum (E 415), flavour sweet and creamy (consist of flavouring substances, maltodextrin (maize), propylene glycol (E 1520) and acacia gum (E 414)).

### What Xarelto looks like and contents of the pack

Xarelto granules for oral suspension are white granules in a glass bottle with child resistant screw cap.

#### Pack sizes

- For children weighing **less than 4 kg**:  
Folding box with one brown glass bottle (100 mL) containing 2.625 g granules (corresponding to 51.7 mg rivaroxaban), two 1 mL blue syringes, one 50 mL water syringe and one adapter.
- For children weighing **4 kg or more**:  
Folding box with one brown glass bottle (250 mL) containing 5.25 g granules (corresponding to 103.4 mg rivaroxaban), two 5 mL and two 10 mL blue syringes, one 100 mL water syringe and one adapter.

Not all pack sizes may be marketed.

The individual weight-adjusted dose volume and frequency should be specified by the prescriber. It should be written on the outer carton when provided to the parents, caregivers or patients.

Please follow carefully the Instructions for Use booklet which is provided in each pack.

Watch the educational video which you can access via the QR code which is displayed on the Patient Alert Card that is provided with this medicine.

### Marketing Authorisation Holder and Manufacturer

Bayer AG  
51368 Leverkusen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België / Belgique / Belgien**

Bayer SA-NV  
Tél/Tel: +32-(0)2-535 63 11

**България**

Байер България ЕООД  
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Tel: +420-266 101 111

**Danmark**

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**Deutschland**

Bayer Vital GmbH  
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**Eesti**

Bayer OÜ  
Tel: +372-655 85 65

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Bayer Ελλάς ABEE  
Τηλ: +30-210-618 75 00

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Tél (N° vert): +33-(0)800 87 54 54

**Hrvatska**

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Icepharma hf.  
Sími: +354-540 80 00

**Italia**

Bayer S.p.A.  
Tel: +39-02-3978 1

**Lietuva**

UAB Bayer  
Tel: +370-5-233 68 68

**Luxembourg / Luxemburg**

Bayer SA-NV  
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Alfred Gera and Sons Ltd.  
Tel: +356-21 44 62 05

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Tel: +31-(0)297-28 06 66

**Norge**

Bayer AS  
Tlf: +47-23 13 05 00

**Österreich**

Bayer Austria Ges. m. b. H.  
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**Polska**

Bayer Sp. z o.o.  
Tel: +48-22-572 35 00

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Bayer Portugal, Lda.  
Tel: +351-21-416 42 00

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SC Bayer SRL  
Tel: +40-(0)21-529 59 00

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Tel: +386-(0)1-58 14 400

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Tel: +421-(0)2-59 21 31 11

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Puh/Tel: +358-(0)20-78521

**Κύπρος**  
NOVAGEM Limited  
Τηλ: +357-22-48 38 58

**Sverige**  
Bayer AB  
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SIA Bayer  
Tel: +371-67 84 55 63

**United Kingdom (Northern Ireland)**  
Bayer AG  
Tel: +44-(0) 118 206 3000

**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency website:  
<http://www.ema.europa.eu>.

## Instructions for Use (IFU)

### Instructions for Use

#### **Xarelto 1 mg/mL**

**100 mL bottle with 2.625 g granules for preparation of oral suspension**

**Active pharmaceutical ingredient: Rivaroxaban**

**Preparation and administration of the oral suspension (granules-water-mixture)**

#### **Glossary and symbols**

- Granules: powder (provided in the bottle) which contains active pharmaceutical ingredient
- Water syringe: 50 mL syringe used to measure and add 50 mL of water to the bottle containing Xarelto granules.
- Suspension: granules-water-mixture (for oral application)
- Blue syringe: syringe with blue plunger to extract and orally administer Xarelto.



Caution: Consult Instructions for Use for relevant information related to warnings and precautions.



Consult Instructions for Use (IFU).



Keep away from sunlight



Protect from moisture



Manufacturing date



Expiry date



Reference number



Batch number



For oral use only

## Before you start

- Read all sections of the Instructions for Use carefully before using Xarelto for the first time and before administering each dose.
- Watch the educational video which you can access via the QR code displayed on the Patient Alert Card that is provided with this medicine.
- Be sure you understand the instructions before starting. If not, call your doctor.
- Further information regarding Xarelto can be found in the Package Leaflet

## Packaging contents

Every Xarelto box contains the following components:



**1 bottle with child resistant screw cap** containing Xarelto granules.



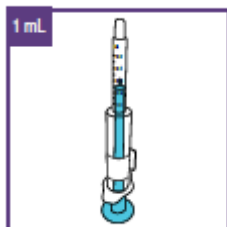
**1 packaged 50 mL water syringe** (for single use only)

The water syringe is used to extract the exact quantity of water required to prepare Xarelto suspension.



**1 packaged bottle adapter**

The adapter is inserted into the neck of the bottle containing Xarelto granules after the exact quantity of water is added to the bottle. This bottle adapter connects the blue syringe to the bottle to ensure the correct amount of suspension can be extracted from the bottle into the blue syringe.



**2 packaged 1 mL blue syringes (one is a spare syringe):**

This blue syringe is used to administer volumes up to **1 mL**

Use the appropriate blue syringe for the volume of suspension that is to be administered.

The blue syringes have a **red** button under the label. This button serves to fix the required dosing volume.

Keep the label at this place on the blue syringe until instructed to remove it.



### 1 Instructions for Use (IFU) (this document)

The IFU contains a description of the preparation of the suspension and how the blue syringe is set up and handled.



### 1 Package Leaflet

Provides important information about Xarelto.



### 1 Patient Alert Card

Important information in case of emergency.

To be kept with the patient at all times and presented to every physician or dentist prior to treatment



### Cautionary Information:

**Do not** unpack the single components until the instructions tell you to do so.

**Do not** use Xarelto if any of the parts have been opened or are damaged.

**Do not** use Xarelto after the expiry date which is stated on the box.

### Warnings and precautions

- **Only** use non-carbonated drinking water to prepare the suspension to avoid bubbles. That means you can use either
  - fresh tap water or
  - non-carbonated (still) mineral water
- It is very important that the precise amount of water is added to the granules in the bottle to ensure the correct concentration of Xarelto.
  - Use the water syringe for measurement of 50 mL water, see below for more information.
  - Measure the amount water to be provided to the bottle very carefully.
- After preparation the suspension can be used for 14 days if stored at room temperature. Ensure to write the expiry date of the suspension (date of preparation plus 14 days) on the dedicated field on the bottle label.
- **Do not** store the suspension above 30 °C. **Do not** freeze.  
If the suspension has been stored in the refrigerator, allow the suspension to adjust to room temperature before extracting the relevant dose.
- Shake the suspension for initial preparation **for at least 60 seconds**.
- Shake the suspension in the bottle **for at least 10 seconds** before each administration.
- It is very important that the prescribed dose volume of Xarelto is being administered.
  - Make sure that you know the prescribed dose and frequency of administration. Ask your doctor or pharmacist if you do not know the prescribed dose and frequency.
  - Carefully adjust the blue syringe according the prescribed volume.
  - Administer the prescribed dose by using the blue syringe. Follow the doctor's instructions

- on how often per day you should administer the prescribed dose.
  - Check for air bubbles in the blue syringe before administration of the oral suspension.
- If your child repeatedly does not take all the required dose or spits some of it out, call your child's doctor to find out what to do.
- Between dosing, store the oral suspension out of sight and reach of children.
- Keep the Instructions for Use so that you can refer to them later during the use of Xarelto.

## Using Xarelto

- Xarelto suspension is for oral use only.
- Volume and frequency of administration of Xarelto depend on your child's weight, so it will change over time if your child will receive Xarelto for a longer time.
  - Your child's doctor will tell you the right dose volume .
  - Do not change the dose yourself.**
  - Always** use the volume prescribed by your child's doctor and have the correct dosing of administration written on the designated field on the outside of the box.  
If it is not written on the field, ask your child's doctor or pharmacist to provide the relevant information.
- Follow the detailed Instructions for Use given in the chapters below.
- Take care to comply with the instructions concerning administration:
  - Intake: Three times a day
  - Administration: Approximately 8 hours apart with feeding

## 1. Preparing the oral suspension

### Step 1.1: Preparation – Get ready

The preparation of the suspension is done once with every new package.  
Before preparing the suspension:



a. Thoroughly wash your hands with soap and dry them afterwards



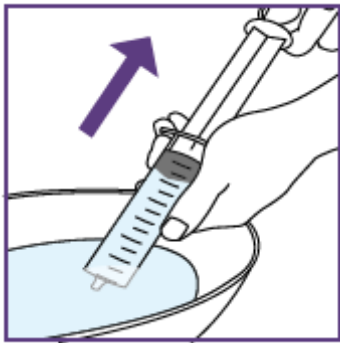
b. Check the expiry date on the label provided on the box.  
**Do not** use the medicine if the medicine has expired.

- c. Obtain the following additional items:
- Container with at least 150 mL of water:
    - Either fresh tap water or non-carbonated (still) mineral water
    - Water should be at room temperature
  - Tissue for soaking up any excess water

### Step 1.2: Filling the required volume of water

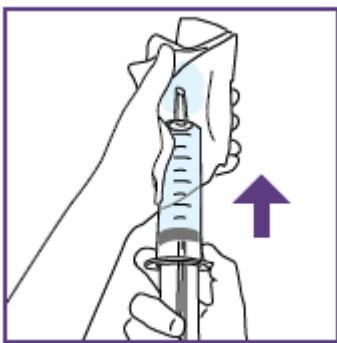
Every time you start a new pack, use only the new materials contained in the new package.

- a. Unpack the water syringe.



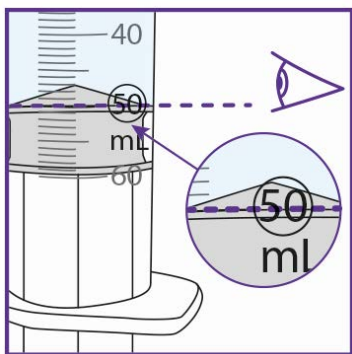
- b. Dip the opening of the water syringe into the container with water.
- c. Extract a volume of more than 50 mL.  
To do this, pull the plunger rod towards you, and make sure that the opening of the water syringe stays below the water surface all the time. This will avoid air bubbles in the syringe.
- d. Take the syringe out of the water.

- e. Turn the water syringe in a way that the opening is facing upwards.  
→ Any air bubbles will move to the top when holding the syringe upwards.  
Tap it with your fingers to further move any air bubble to the top.



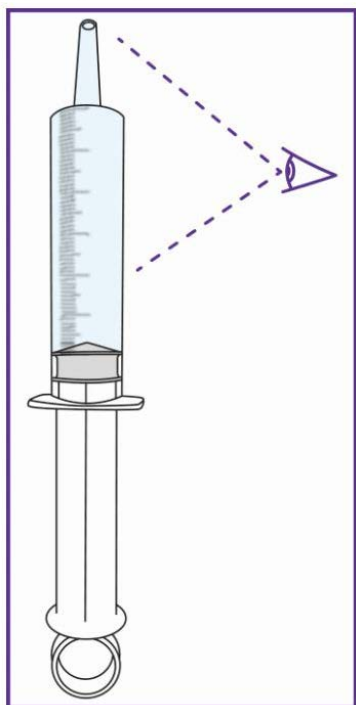
- f. Push the plunger rod until the upper ring of the plunger reaches the 50 mL mark.  
→ When pressing the plunger, water can come out of the tip of the water syringe. This waste water can be soaked up with a tissue.





### Cautionary Information:

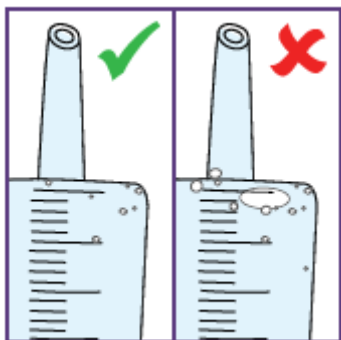
The upper ring of the black plunger **must be precisely in line with the 50 mL mark** to be able to achieve the correct concentration of the suspension.



g. Continue to hold the water syringe with the opening facing upwards and check the water in the syringe carefully:

- for correct volume,
- for air bubbles.

Small air bubbles are uncritical, but big air bubbles are critical. See below for more explanation on what to do.



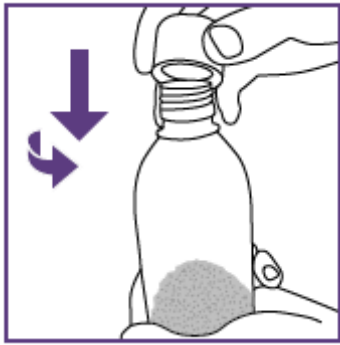
h. **If the syringe is not loaded correctly or contains too much air:**

- Empty the water syringe
- Repeat steps b. to h

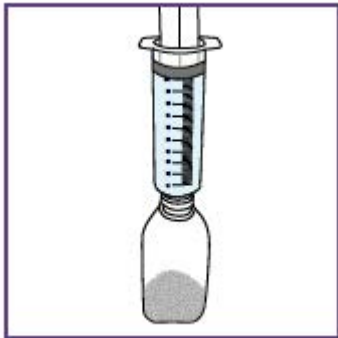
### Step 1.3: Adding water to the granules

a. **If the granules in the bottle appear to be clumpy:**

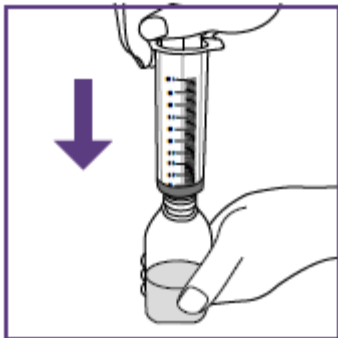
- Gently tap the bottle on your hand.
- **Be careful** since the bottle is made of glass.



- b. Unscrew the child resistant cap of the bottle (push down and turn counterclockwise).



- c. Place the filled water syringe on the upper edge of the bottle opening

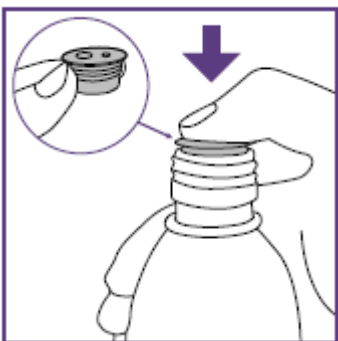


- d. Hold the bottle firmly.  
e. Press the plunger rod down slowly.  
**The full volume of water must be transferred to the bottle.**  
f. Dispose of the water syringe in household waste.

#### Step 1.4: Fitting the adapter and mixing the oral suspension

The adapter is used to fill the blue syringe with suspension.

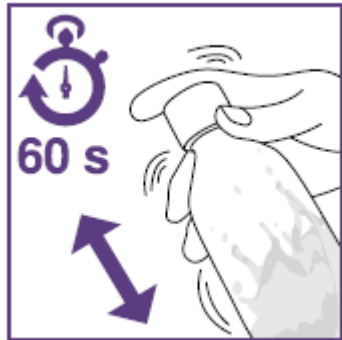
- a. Unpack the bottle adapter



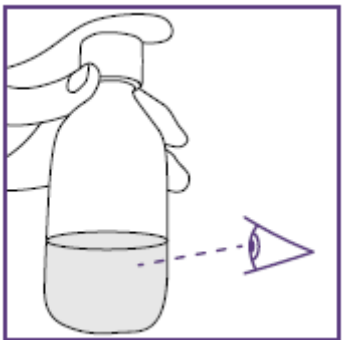
- b. Push the adapter completely into the neck of the bottle



c. Close the bottle tightly with the screw cap.



d. Shake the bottle **gently** for **at least 60 seconds**.  
→ This is intended to provide a well-mixed suspension.



e. Check whether the suspension is thoroughly mixed:

- no clumps
- no deposit.



#### Cautionary Information:

To guarantee correct dose, the suspension must **not** contain **any** clumps or deposit.

f. **If there are clumps or sediment** repeat steps d. to f.

→ When no clumps or deposits are left, the suspension is ready for use.

**Do not add more water to the bottle.**

The suspension has a shelf life of 14 days at room temperature.



g. Write the date of expiry of the just prepared suspension on the label of the bottle.

**Date of preparation + 14 days**

The shown pictogram is only an example.

## 2. Setting the prescribed dose with every new blue syringe

**To prevent overdosing or underdosing an exact dose of suspension is required.**

Before you take the first dose out of the bottle, the enclosed blue syringe must be set up in accordance with the dose prescribed by your child's doctor. This information can be found on the dedicated area of the box. If no information has been entered here check back with the child's doctor or pharmacist.

After setting the dose the same blue syringe can be used for all administrations from the bottle of suspension prepared in step 1.

**Once the dose has been fixed on the blue syringe, it cannot be changed.**

The blue syringe features a scale (mL).

The scale of the 1 mL blue syringe starts with 0.2 mL.

The graduation marks are in increments of 0.1 mL.

**Note:**

**Do not remove the peelable label until you are prompted in the Instructions for Use.**

The blue syringe features a **red** button to adjust the volume. This button is initially covered by a peelable label.

By pressing the red button the volume of the syringe is set, which can only be done once. **Do not** press the **red** button until the Instructions for Use tell you to do so.

Once the **red** button has been pressed, the volume can no longer be adjusted.

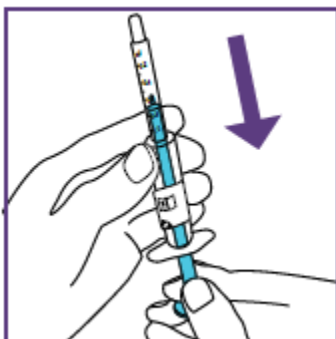


- a. Review the dose provided in the respective field on the outside of the box.

**b. If the information is not available:**

Ask your pharmacist or doctor to provide it.

- c. Hold the blue syringe with the opening pointing upwards



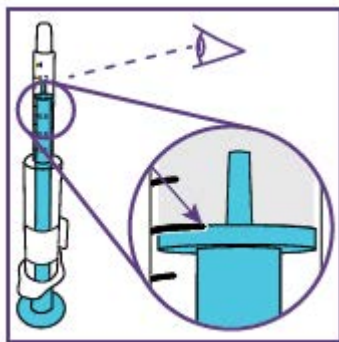
- d. Pull the plunger rod **slowly** until the upper margin reaches the mark of the volume to be administered.

→ When moving the plunger rod, you can hear a “Click” for each adjustable volume step.



**Cautionary Information:**

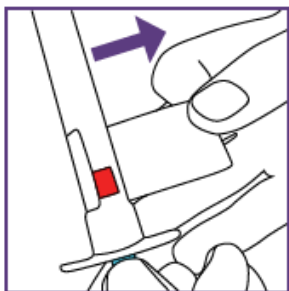
The upper edge of the plunger **must be exactly in line** with the correct mark of the volume to be administered.



The shown pictogram is only an example. Your volume might be different.

**Be careful, do not** pull the plunger past the volume to be administered.

**Be careful, do not** press on the label when pulling the plunger.



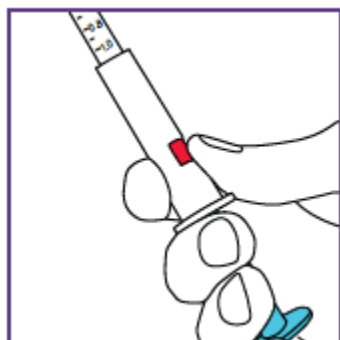
e. Remove the label of the blue syringe **completely**.

→ You can now see the **red** button for setting the volume.

f. Check the position of the plunger again. Ensure the upper edge of the plunger is exactly in line with the correct mark of the volume to be administered.

g. **If the position of the blue plunger does not match the required volume:**

Adjust it accordingly



h. If the position of the blue plunger matches the required volume, push the **red** button to fix the adjustment.

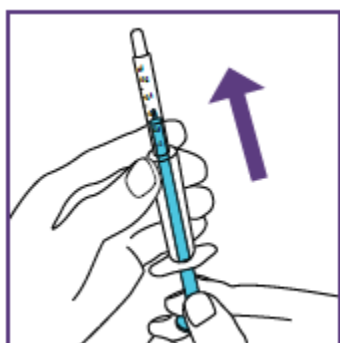
→ The required dose is now set.

→ Pressing the red button will produce another clicking sound. The clicking sound will not be audible afterwards.



#### Cautionary Information:

If you notice that the wrong dose has been selected (the red button has been pushed, when the plunger was in the wrong position) use the appropriate spare blue syringe. Repeat steps a. to h. with a new blue syringe.



i. Push the plunger upwards in the blue syringe as far as it goes.

The blue syringe can now be used.

### 3. Administering the oral suspension

Follow the steps described below for each required administration.

#### Step 3.1: Mixing the oral suspension



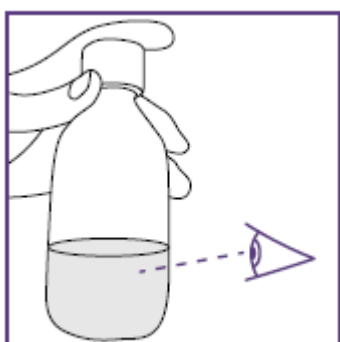
### Cautionary Information:

Allow the suspension to adjust to room temperature if it has been stored in the refrigerator.



a. **Gently** shake the bottle for **at least 10 seconds** before each dose.

→ This is intended to provide a well-mixed suspension.



b. Check whether the suspension is mixed thoroughly, i.e.:

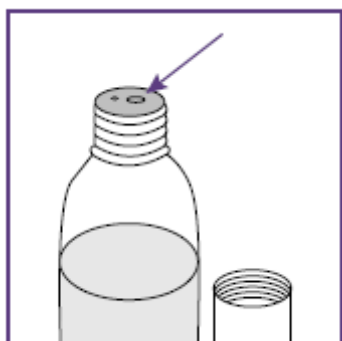
- no clumps
- no deposit.

c. **If there are clumps or deposit:**

Repeat steps a. and b.

d. Shaking can lead to formation of foam.

Let the bottle stand until the foam dissolves.



e. Unscrew the bottle cap, but keep the adapter on the top of the bottle.

**Note:**

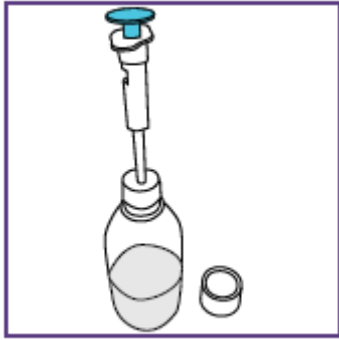
The larger opening visible on the adapter is used to connect the blue syringe.

The surface of the bottle adapter should be free of liquid.

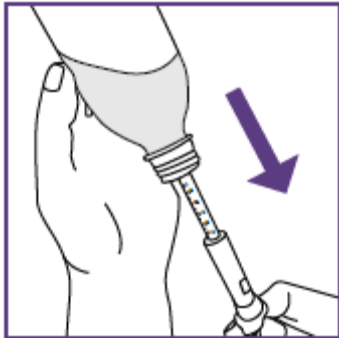
f. **If there is any liquid on the adapter:**

Remove the liquid with a clean tissue

### Step 3.2: Extracting the required dose

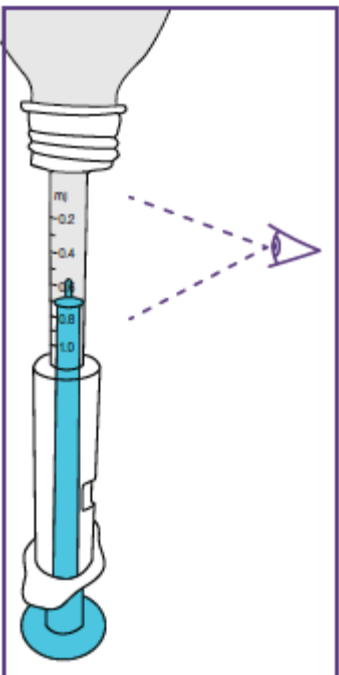


a. Keep the bottle in the upright position. Insert the tip of the blue syringe **fully** into the large opening of the adapter

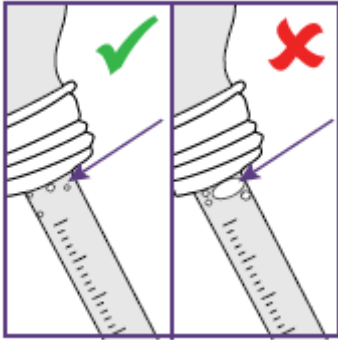


b. Turn the bottle upside down.

c. Pull the blue plunger rod **slowly** until it stops (i.e. until the set dose is reached).



d. Carefully check for air in the blue syringe. Smaller air bubbles are not critical.

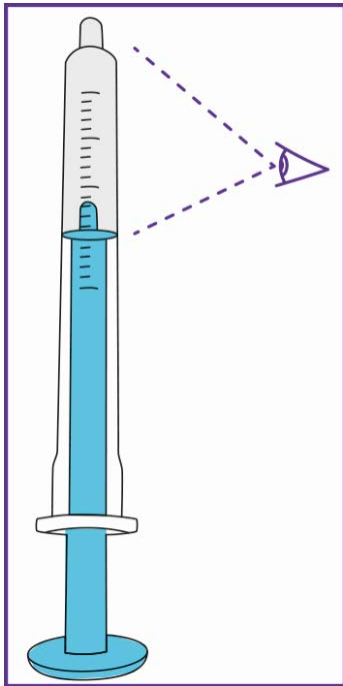


**e. If there are bigger air bubbles:**

- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as possible.
- Repeat steps b. to e.

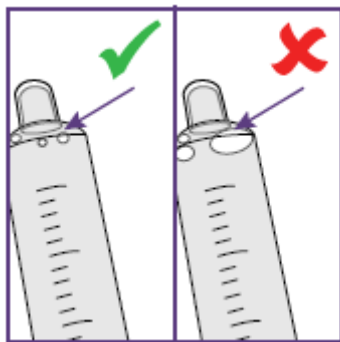
f. Return the bottle to the upright position.

g. Remove the blue syringe **carefully** from the adapter



**h. Hold the blue syringe upright and check:**

- that the tip of the blue syringe is filled
- whether the right dose has been filled into the blue syringe
- that no big air bubbles are present.



**i. If there are bigger air bubbles or air in the tip:**

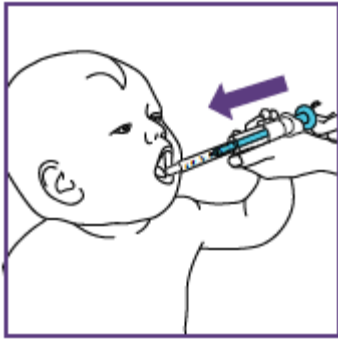
- Insert the tip of the blue syringe again fully into the large opening of the adapter
- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as it goes.
- Repeat steps b. to h. until no bigger air bubbles are visible.

j. Close the bottle with the screw cap.

Administer the suspension immediately after filling the blue syringe (step 3.3)

**Step 3.3: Administration of prescribed dose**





- a. Place the blue syringe into the mouth of the patient.
- b. Direct its tip into the cheek to allow for natural swallowing.
- c. Push the plunger rod down **slowly** until the plunger stops (blue syringe is completely empty).
- d. Ensure that the patient swallows the entire dose.



#### Cautionary Information:

**The patient must swallow the full dose of medicine.**

If the dose repeatedly is not completely swallowed or if the patient is vomiting, consult your doctor for further instructions.



- e. Encourage the patient to drink one typical serving of liquid.
  - For an infant of 6 months, for example, this may be 20 mL.
  - This can also be breast-feeding.

## 4. Cleaning and storage

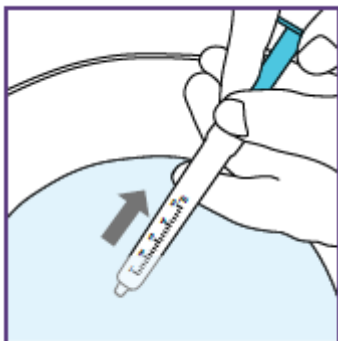
**The blue syringe must be cleaned following every application.**

Follow the steps listed below to clean the device. Altogether, **three** cycles of cleaning are necessary to ensure proper cleaning.

Before you start, you will need the following equipment for step 4.1:

- Get two containers (such as a cup or bowl)
  - one container filled with drinking water,
  - the other container empty

### Step 4.1: Cleaning



- a. Dip the tip of the blue syringe into the container of water.
- b. Withdraw water until plunger rod stops.



c. Empty the blue syringe into the prepared empty container

d. Repeat steps a. to c. an **additional two times**.

e. After cleaning, push the plunger rod back in until it stops.

f. Dry the outer surface of the syringe with a clean tissue



#### Cautionary Information:

- Do not clean the blue syringe in the dish washer.
- Never boil the blue syringe.

### Step 4.2: Storage

Store the blue syringe in a clean and dry place until next use, e.g. keep it in the box Xarelto was given to you.

Keep away from sunlight.



#### Cautionary Information:

The blue syringe **can be used for up to 14 days**.

Store the suspension below 30 °C.



#### Cautionary Information:

**Do not** freeze the suspension.

The prepared suspension is stable at room temperature for up to 14 days (preparation date plus 14 days).

**Keep Xarelto out of the sight and reach of children.**

Store the prepared suspension upright.

### 5. Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## Instructions for Use (IFU)

### Instructions for Use

#### **Xarelto 1 mg/mL**

**250 mL bottle with 5.25 g granules for preparation of oral suspension**

**Active pharmaceutical ingredient: Rivaroxaban**

**Preparation and administration of the oral suspension (granules-water-mixture)**

#### **Glossary and symbols**

- Granules: powder (provided in the bottle) which contains active pharmaceutical ingredient
- Water syringe: 100 mL syringe used to measure and add 100 mL of water to the bottle containing Xarelto granules.
- Suspension: granules-water-mixture (for oral application)
- Blue syringe: syringe with blue plunger to extract and orally administer Xarelto.



Caution: Consult Instructions for Use for relevant information related to warnings and precautions.



Consult Instructions for Use (IFU).



Keep away from sunlight



Protect from moisture



Manufacturing date



Expiry date



Reference number



Batch number



For oral use only

## Before you start

- Read all sections of the Instructions for Use carefully before using Xarelto for the first time and before administering each dose.
- Watch the educational video which you can access via the QR code displayed on the Patient Alert Card that is provided with this medicine.
- Be sure you understand the instructions before starting. If not, call your doctor.
- Further information regarding Xarelto can be found in the Package Leaflet

## Packaging contents

Every Xarelto box contains the following components:



**1 bottle with child resistant screw cap** containing Xarelto granules.



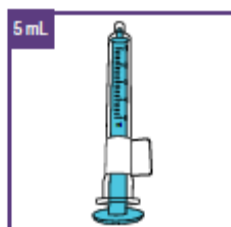
**1 packaged 100 mL water syringe** (for single use only)

The water syringe is used to extract the exact quantity of water required to prepare Xarelto suspension.



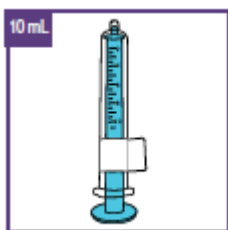
**1 packaged bottle adapter**

The adapter is inserted into the neck of the bottle containing Xarelto granules after the exact quantity of water is added to the bottle. This bottle adapter connects the blue syringe to the bottle to ensure the correct amount of suspension can be extracted from the bottle into the blue syringe.



**2 packaged 5 mL blue syringes (one is a spare syringe) :**

This blue syringe is used to administer volumes up to **5 mL**



## **2 packaged 10 mL blue syringes (one is a spare syringe):**

This blue syringe is used to administer volumes of **5 mL** up to **10 mL**.

Use the appropriate blue syringe for the volume of suspension that is to be administered.

The blue syringes have a **red** button under the label. This button serves to fix the required dosing volume.

Keep the label at this place on the blue syringe until instructed to remove it.



## **1 Instructions for Use (IFU) (this document)**

The IFU contains a description of the preparation of the suspension and how the blue syringe is set up and handled.



## **1 Package Leaflet**

Provides important information about Xarelto.



## **1 Patient Alert Card**

Important information in case of emergency.

To be kept with the patient at all times and presented to every physician or dentist prior to treatment

	<b>Cautionary Information:</b>
<p><b>Do not</b> unpack the single components until the instructions tell you to do so.</p> <p><b>Do not</b> use Xarelto if any of the parts have been opened or are damaged.</p> <p><b>Do not</b> use Xarelto after the expiry date which is stated on the box.</p>	

## **Warnings and precautions**

- **Only** use non-carbonated drinking water to prepare the suspension to avoid bubbles. That means you can use either
  - fresh tap water or
  - non-carbonated (still) mineral water
- It is very important that the precise amount of water is added to the granules in the bottle to ensure the correct concentration of Xarelto.
  - Use the water syringe for measurement of 100 mL water, see below for more information.

- Measure the amount water to be provided to the bottle very carefully.
- After preparation the suspension can be used for 14 days if stored at room temperature. Ensure to write the expiry date of the suspension (date of preparation plus 14 days) on the dedicated field on the bottle label.
- Do not** store the suspension above 30 °C. **Do not** freeze.  
If the suspension has been stored in the refrigerator, allow the suspension to adjust to room temperature before extracting the relevant dose.
- Shake the suspension for initial preparation **for at least 60 seconds**.
- Shake the suspension in the bottle **for at least 10 seconds** before each administration.
- It is very important that the prescribed dose volume of Xarelto is being administered.
  - Make sure that you know the prescribed dose and frequency of administration. Ask your doctor or pharmacist if you do not know the prescribed dose and frequency.
  - Carefully adjust the blue syringe according the prescribed volume.
  - Administer the prescribed dose by using the blue syringe. Follow the doctor's instructions on how often per day you should administer the prescribed dose.
  - Check for air bubbles in the blue syringe before administration of the oral suspension.
- If your child repeatedly does not take all the required dose or spits some of it out, call your child's doctor to find out what to do.
- Between dosing, store the oral suspension out of sight and reach of children.
- Keep the Instructions for Use so that you can refer to them later during the use of Xarelto.

## Using Xarelto

- Xarelto suspension is for oral use only.
- Volume and frequency of administration of Xarelto depend on your child's weight, so it will change over time if your child will receive Xarelto for a longer time.
  - Your child's doctor will tell you the right dose volume and the frequency of administration.
  - Do not change the dose yourself.**
  - Always** use the volume prescribed by your child's doctor and have the correct dosing and frequency of administration written on the designated field on the outside of the box.  
If it is not written on the field, ask your child's doctor or pharmacist to provide the relevant information.
- Follow the detailed Instructions for Use given in the chapters below.
- Take care to comply with the instructions concerning administration:

Intake	Administration time point	Time span between administrations
once a day	with feeding or with a meal	approximately 24 hours apart
twice a day		approximately 12 hours apart
three times a day		approximately 8 hours apart

## 1. Preparing the oral suspension

### Step 1.1: Preparation – Get ready

The preparation of the suspension is done once with every new package.  
Before preparing the suspension:



a. Thoroughly wash your hands with soap and dry them afterwards.



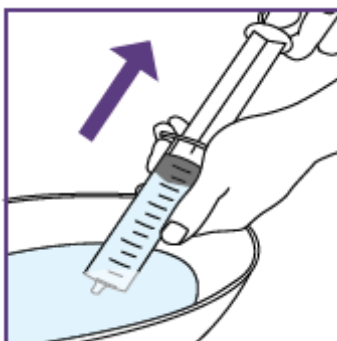
b. Check the expiry date on the label provided on the box.  
**Do not** use the medicine if the medicine has expired.

c. Obtain the following additional items:

- Container with at least 150 mL of water:
  - Either fresh tap water or non-carbonated (still) mineral water
  - Water should be at room temperature
- Tissue for soaking up any excess water

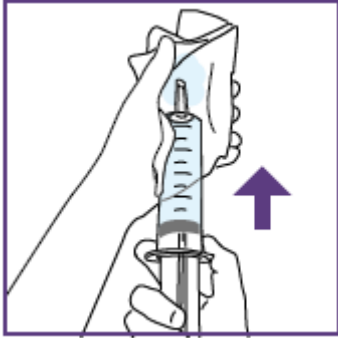
### Step 1.2: Filling the required volume of water

Every time you start a new pack, use only the new materials contained in the new package.

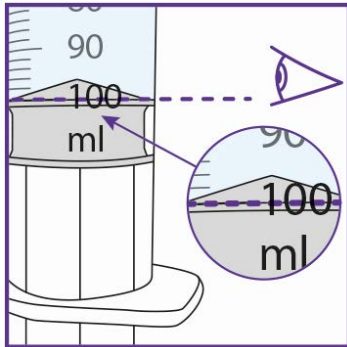


- a. Unpack the water syringe.
- b. Dip the opening of the water syringe into the container with water.
- c. Extract a volume of more than 100 mL.  
To do this, pull the plunger rod towards you, and make sure that the opening of the water syringe stays below the water surface all the time. This will avoid air bubbles in the syringe.
- d. Take the syringe out of the water.

- e. Turn the water syringe in a way that the opening is facing upwards.  
→ Any air bubbles will move to the top when holding the syringe upwards.  
Tap it with your fingers to further move any air bubble to the top.

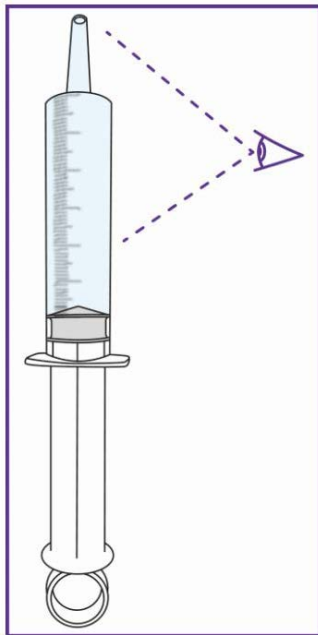


- f. Push the plunger rod until the upper ring of the plunger reaches the 100 mL mark.  
→ When pressing the plunger, water can come out of the tip of the water syringe. This waste water can be soaked up with a tissue.



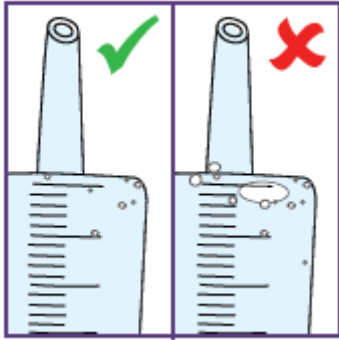
**Cautionary Information:**

The upper ring of the black plunger **must be precisely in line with the 100 mL** mark to be able to achieve the correct concentration of the suspension.



- g. Continue to hold the water syringe with the opening facing upwards and check the water in the syringe carefully:
- for correct volume,
  - for air bubbles.
- Small air bubbles are uncritical, but big air bubbles are critical. See below for more explanation on what to do.





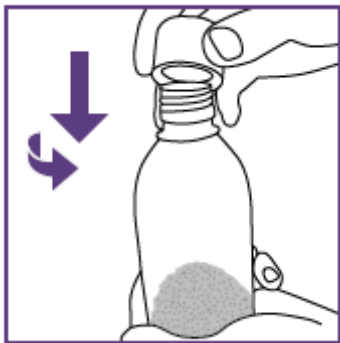
h. **If the syringe is not loaded correctly or contains too much air:**

- Empty the water syringe
- Repeat steps b. to h

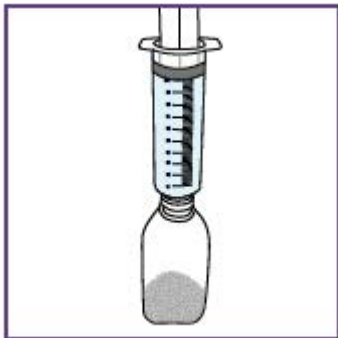
### Step 1.3: Adding water to the granules

a. **If the granules in the bottle appear to be clumpy:**

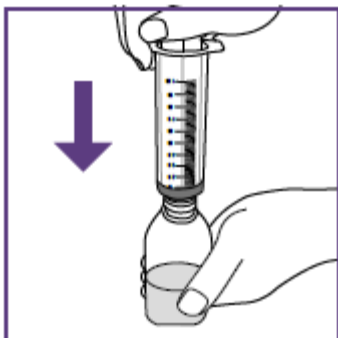
- Gently tap the bottle on your hand.
- **Be careful** since the bottle is made of glass.



b. Unscrew the child resistant cap of the bottle (push down and turn counterclockwise).



c. Place the filled water syringe on the upper edge of the bottle opening



d. Hold the bottle firmly.

e. Press the plunger rod down slowly.

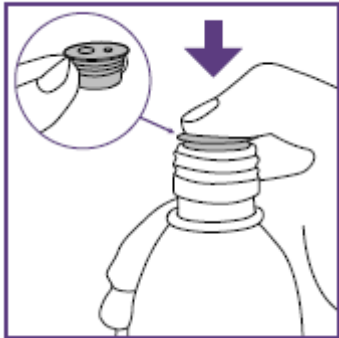
**The full volume of water must be transferred to the bottle.**

f. Dispose of the water syringe in household waste.

### Step 1.4: Fitting the adapter and mixing the oral suspension

The adapter is used to fill the blue syringe with suspension.

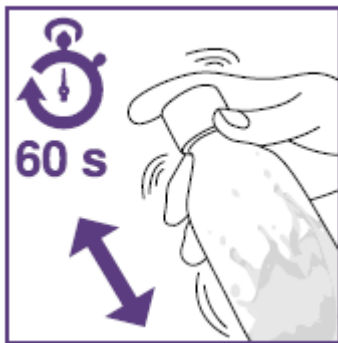
- a. Unpack the bottle adapter
- b. Push the adapter completely into the neck of the bottle



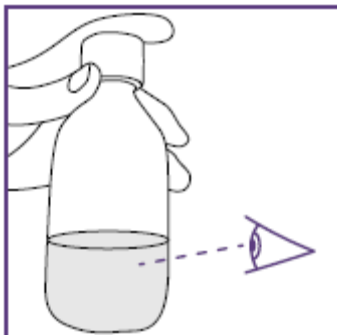
- c. Close the bottle tightly with the screw cap.



- d. Shake the bottle **gently** for **at least 60 seconds**.  
→ This is intended to provide a well-mixed suspension.



- e. Check whether the suspension is thoroughly mixed:
  - no clumps
  - no deposit.



#### Cautionary Information:

To guarantee correct dose, the suspension must **not** contain **any** clumps or deposit.

- f. If there are **clumps or sediment** repeat steps d. to f.

→ When no clumps or deposits are left, the suspension is ready for use.

**Do not add more water to the bottle.**

The suspension has a shelf life of 14 days at room temperature.



- g. Write the date of expiry of the just prepared suspension on the label of the bottle.

**Date of preparation + 14 days**

The shown pictogram is only an example.

## 2. Setting the prescribed dose with every new blue syringe

**To prevent overdosing or underdosing an exact dose of suspension is required.**

Before you take the first dose out of the bottle, the enclosed blue syringe must be set up in accordance with the dose prescribed by your child's doctor. This information can be found on the dedicated area of the box. If no information has been entered here check back with the child's doctor or pharmacist.

After setting the dose the same blue syringe can be used for all administrations from the bottle of suspension prepared in step 1.

**Once the dose has been fixed on the blue syringe, it cannot be changed.**

### Step 2.1: Selecting a suitable blue syringe

Dosing devices with different capacities are included in this pack:

**5 mL blue syringes** for doses from **1 mL to 5 mL**

**10 mL blue syringes** for doses from **5 mL to 10 mL**

- a. Select the suitable blue syringe based on the dose prescribed by your child's doctor.

The other blue syringes are not needed.

- b. Unpack the blue syringe.

**Note:**

**Do not remove the peelable label until you are prompted in the Instructions for Use.**

The blue syringe features a **red** button to adjust the volume. This button is initially covered by a peelable label.

By pressing the red button the volume of the syringe is set, which can only be done once. **Do not** press the **red** button until the Instructions for Use tell you to do so.

Once the **red** button has been pressed, the volume can no longer be adjusted.

### Step 2.2: Setting the required dose on new blue syringe

The blue syringe features a scale (mL).

The scale of the 5 mL blue syringe starts with 1 mL. The graduation marks are in increments of 0.2 mL.

The scale of the 10 mL blue syringe starts with 2 mL. The graduation marks are in increments of 0.5 mL.



- a. Review the dose provided in the respective field on the outside of the box.

**Note:**

Use the 10 mL blue syringe for prescribed doses larger than 10 mL as follows:

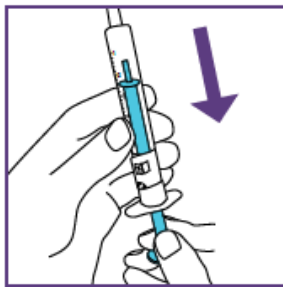
Dose of 15 mL: 2 x 7.5 mL blue syringe

Dose of 20 mL: 2 x 10 mL blue syringe

- b. **If the information is not available:**

Ask your pharmacist or doctor to provide it.

- c. Hold the blue syringe with the opening pointing upwards



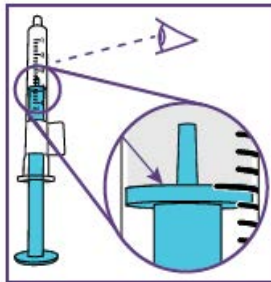
- d. Pull the plunger rod **slowly** until the upper margin reaches the mark of the volume to be administered.

→ When moving the plunger rod, you can hear a “Click” for each adjustable volume step.



**Cautionary Information:**

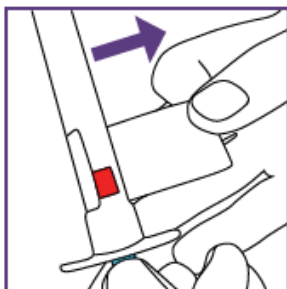
The upper edge of the plunger **must be exactly in line** with the correct mark of the volume to be administered.



The shown pictogram is only an example. Your volume might be different.

**Be careful, do not** pull the plunger past the volume to be administered.

**Be careful, do not** press on the label when pulling the plunger.



- e. Remove the label of the blue syringe **completely**.

→ You can now see the **red** button for setting the volume.

- f. Check the position of the plunger again. Ensure the upper edge of the plunger is exactly in line with the correct mark of the volume to be administered.

- g. **If the position of the blue plunger does not match the required volume:**

Adjust it accordingly

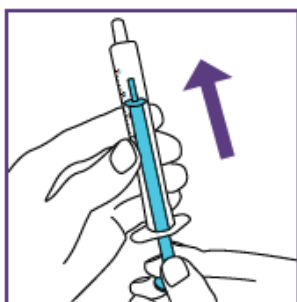


- h. If the position of the blue plunger matches the required volume, push the **red** button to fix the adjustment.
- The required dose is now set.
  - Pressing the red button will produce another clicking sound.
  - The clicking sound will not be audible afterwards.



#### Cautionary Information:

If you notice that the wrong dose has been selected (the red button has been pushed, when the plunger was in the wrong position) use the appropriate spare blue syringe. Repeat steps a. to h. with a new blue syringe.



- i. Push the plunger upwards in the blue syringe as far as it goes. The blue syringe can now be used.

### 3. Administering the oral suspension

Follow the steps described below for each required administration.

#### Step 3.1: Mixing the oral suspension

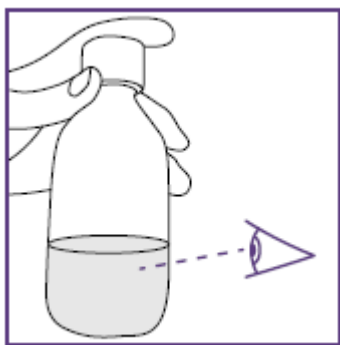


#### Cautionary Information:

Allow the suspension to adjust to room temperature if it has been stored in the refrigerator.



- a. **Gently** shake the bottle for **at least 10 seconds** before each dose.
- This is intended to provide a well-mixed suspension.



b. Check whether the suspension is mixed thoroughly, i.e.:

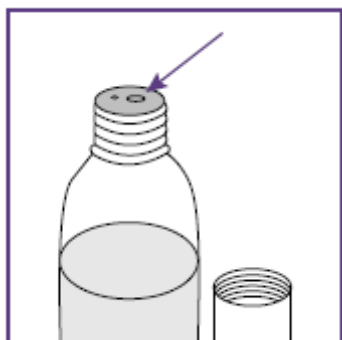
- no clumps
- no deposit.

**c. If there are clumps or deposit:**

Repeat steps a. and b.

d. Shaking can lead to formation of foam.

Let the bottle stand until the foam dissolves.



e. Unscrew the bottle cap, but keep the adapter on the top of the bottle.

**Note:**

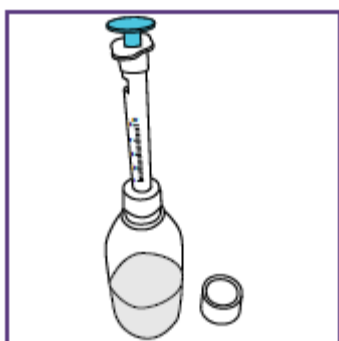
The larger opening visible on the adapter is used to connect the blue syringe.

The surface of the bottle adapter should be free of liquid.

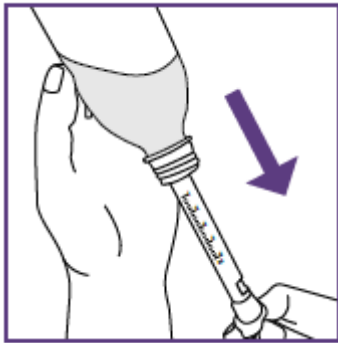
**f. If there is any liquid on the adapter:**

Remove the liquid with a clean tissue

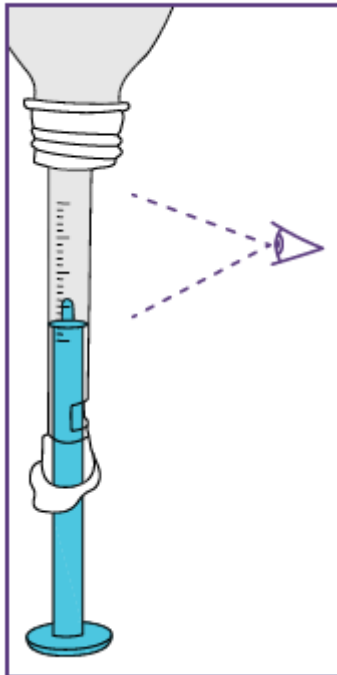
### Step 3.2: Extracting the required dose



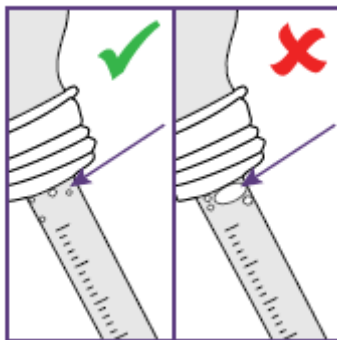
a. Keep the bottle in the upright position. Insert the tip of the blue syringe **fully** into the large opening of the adapter



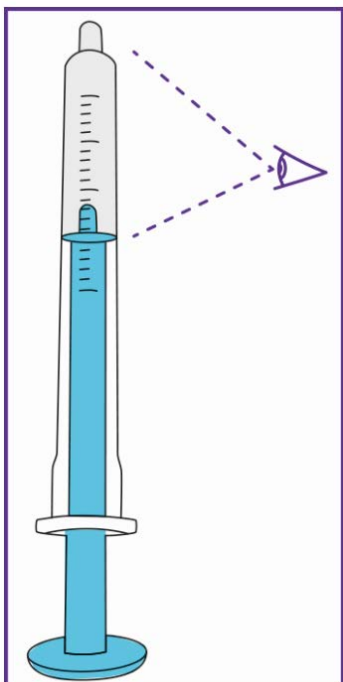
- b. Turn the bottle upside down.  
 c. Pull the blue plunger rod **slowly** until it stops (i.e. until the set dose is reached).



- d. Carefully check for air in the blue syringe.  
 Smaller air bubbles are not critical.

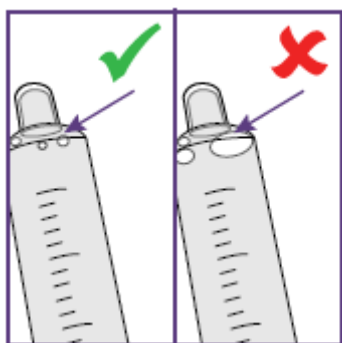


- e. **If there are bigger air bubbles:**
- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as possible.
  - Repeat steps b. to e.
- f. Return the bottle to the upright position.  
 g. Remove the blue syringe **carefully** from the adapter



h. Hold the blue syringe upright and check:

- that the tip of the blue syringe is filled
- whether the right dose has been filled into the blue syringe
- that no big air bubbles are present.



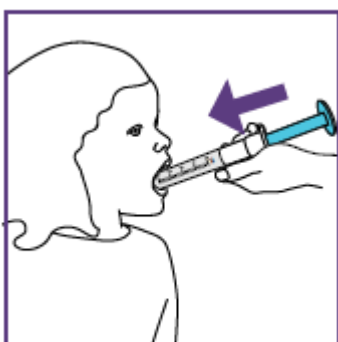
i. If there are bigger air bubbles or air in the tip:

- Insert the tip of the blue syringe again fully into the large opening of the adapter
- Return the suspension to the bottle by pushing back the plunger rod into the blue syringe as far as it goes.
- Repeat steps b. to h. until no bigger air bubbles are visible.

j. Close the bottle with the screw cap.

Administer the suspension immediately after filling the blue syringe (step 3.3)

### Step 3.3: Administration of prescribed dose



- Place the blue syringe into the mouth of the patient.
- Direct its tip into the cheek to allow for natural swallowing.
- Push the plunger rod down **slowly** until the plunger stops (blue syringe is completely empty).
- Ensure that the patient swallows the entire dose.



#### Cautionary Information:

**The patient must swallow the full dose of medicine.**

If the dose repeatedly is not completely swallowed or if the patient is vomiting, consult your doctor for further instructions.





- e. Encourage the patient to drink one typical serving of liquid.
- For an infant of 6 months, for example, this may be 20 mL.
  - This can also be breast-feeding.
  - For an adolescent it may be a volume up to 240 mL

#### 4. Cleaning and storage

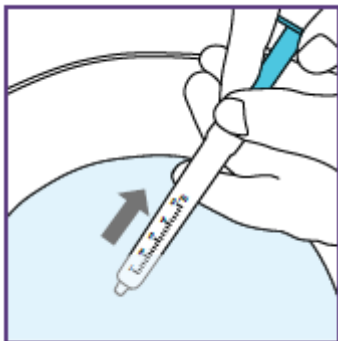
**The blue syringe must be cleaned following every application.**

Follow the steps listed below to clean the device. Altogether, **three** cycles of cleaning are necessary to ensure proper cleaning.

Before you start, you will need the following equipment for step 4.1:

- Get two containers (such as a cup or bowl)
  - one container filled with drinking water,
  - the other container empty

##### Step 4.1: Cleaning




- a. Dip the tip of the blue syringe into the container of water.  
b. Withdraw water until plunger rod stops.



- c. Empty the blue syringe into the prepared empty container


- d. Repeat steps a. to c. an **additional two times**.  
e. After cleaning, push the plunger rod back in until it stops.  
f. Dry the outer surface of the syringe with a clean tissue

	<b>Cautionary Information:</b>
<ul style="list-style-type: none"> <li>▪ Do not clean the blue syringe in the dish washer.</li> <li>▪ Never boil the blue syringe.</li> </ul>	


#### Step 4.2: Storage

Store the blue syringe in a clean and dry place until next use, e.g. keep it in the box Xarelto was given to you.

Keep away from sunlight.

	<b>Cautionary Information:</b>
The blue syringe <b>can be used for up to 14 days.</b>	

Store the suspension below 30 °C.

	<b>Cautionary Information:</b>
<p><b>Do not</b> freeze the suspension.</p> <p>The prepared suspension is stable at room temperature for up to 14 days (preparation date plus 14 days).</p> <p><b>Keep Xarelto out of the sight and reach of children.</b></p> <p>Store the prepared suspension upright.</p>	

#### 5. Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

#### **Annex IV**

**Scientific conclusions and grounds for the variation to the terms of the marketing  
authorisation(s)**

## **Scientific conclusions**

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final study report for the medicinal product(s) mentioned above, the scientific conclusions of CHMP are as follows:

The PRAC considered it appropriate to summarise the key results from this imposed PASS program, which had been conducted in 3 EU countries and the UK, and which comprised more than 40,000 patients in the VTE-T indication and 162,000 patients in the NVAF indication, and reflect those in the SmPC, section 5.1 Pharmacodynamic properties of the product information.

Furthermore, by finalisation of this category 1 study program, removal of the additional monitoring statement and the black triangle from the product information is warranted. Annex II of the product information should also be updated to remove this condition.

Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information and changes to the conditions of the marketing authorisation were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

## **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) mentioned above, the CHMP is of the opinion that the benefit-risk balance of these medicinal product(s) is unchanged, subject to the proposed changes to the product information.

The CHMP is of the opinion that the terms of the marketing authorisation(s) of the medicinal product(s) mentioned above should be varied.