



XARELTO®

Film-coated Tablet

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.

Each 2.5 mg film-coated tablet contains 35.70 mg lactose monohydrate

For a full list of excipient(s) see section 6

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), is indicated for the prevention of major atherothrombotic events (cardiovascular death, myocardial infarction & stroke) in adult patients with coronary artery disease (CAD) and/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.

- CAD and/or PAD

Patients taking Xarelto 2.5 mg twice daily should also take a daily dose of 100 mg ASA.

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.

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 ≥ 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 in children aged 0 to 18 years have not been established. No data are available. Therefore, Xarelto is 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).

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 Xarelto tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (see section 5.2).

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

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.

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. 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 section 4.5).

Patients on treatment with Xarelto and ASA 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

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).

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

- ≥ 75 years of age if co-administered with ASA. 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

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

CAD and/or 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).

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 with ASA in these situations.

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

Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

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.

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.

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.

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 phase III studies including 53,103 patients exposed to rivaroxaban (see Table 1).

Table 1 : Number of patients studied, total daily dose and maximum treatment duration in the Xarelto phase III studies as outlined below:

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	10mg	39 days
Prevention of VTE in medically ill patients	3,997	10mg	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 six months: 10 mg or 20 mg	21 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 or PAD	18,244	5 mg in combination with 100 mg ASA or 10 mg alone	47 months

*Patients exposed to at least one dose of rivaroxaban

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 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
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 and/or PAD	6.7 per 100 patient years	0.15 per 100 patient years**

* 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

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto 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 patients in phase III clinical trials or through post-marketing use*

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) ^A , Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				

Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation ^A , diarrhoea, vomiting ^A	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase ^A , increased GGT ^A	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity ^A	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				

Urogenital tract haemorrhage (incl. haematuria and menorrhagia ^B), renal impairment (incl. blood creatinine increased, blood urea increased) ^A				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever ^A , peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema ^A		
Investigations				
	Increased LDH ^A , increased lipase ^A , increased amylase ^A			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion ^A		Vascular pseudoaneurysm ^c		

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. As incidence of adverse reactions did not increase and no new adverse reaction was identified, COMPASS study data were not included for frequency calculation in this table.

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 Xarelto 2.5mg_BTTF_Apr 2025

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, or anticoagulant-related nephropathy have been reported for Xarelto. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. 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 antidote antagonising the pharmacodynamic effect of rivaroxaban is not available. 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, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these 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

CAD and/or PAD

The phase III COMPASS study (27,395 patients, 78.0% male, 22.0% female) demonstrated the efficacy and safety of Xarelto 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 randomized to pantoprazole or placebo. All patients were then randomized 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 revascularization 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.

Xarelto 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 4 and Figure 1).

There was a significant increase of the primary safety outcome (modified ISTH major bleeding events) in patients treated with Xarelto 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 5).

For the primary efficacy outcome, the observed benefit of Xarelto 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 ≥ 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 ≥ 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%).

Table 4: Efficacy results from phase III COMPASS

Study Population	Patients with CAD and/or PAD ^{a)}					
Treatment Dosage	Xarelto 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 ^{b)}
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 5: Safety results from phase III COMPASS

Study population	Patients with CAD and/or PAD ^{a)}		
Treatment Dose	Xarelto 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)	ASA 100 mg od N=9126 n (Cum.risk %)	Hazard Ratio (95 % CI) p-value ^{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

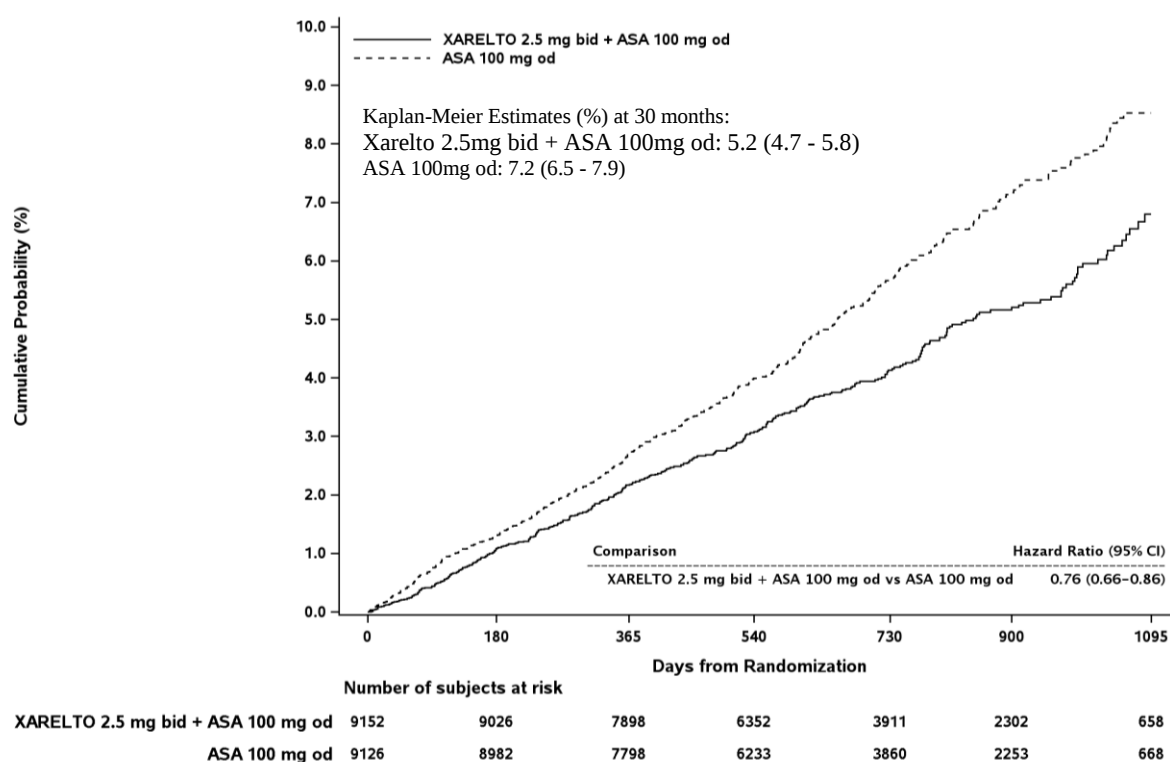
Study population	Patients with CAD and/or PAD ^{a)}		
Treatment Dose	Xarelto 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)	ASA 100 mg od N=9126 n (Cum.risk %)	Hazard Ratio (95 % CI) p-value ^{b)}
- Bleeding into the surgical site requiring reoperation (non- fatal, not in critical 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 1: 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 with high risk triple positive antiphospholipid syndrome

Xarelto 2.5mg_BTF_Apr 2025

In an investigator sponsored, randomized open-label multicenter 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 trial 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 randomized 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 randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomized 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

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.

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).

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. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

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 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 5 cP
Sodium laurilsulphate
Magnesium stearate

Film-coat

Macrogol 3350
Hypromellose 15cP
Titanium dioxide (E 171)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to labels.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

PP/Aluminium foil blisters in cartons of 28,30, 56 or 60 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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