

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 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.

Excipients:

Each film-coated tablet contains 27.9 mg lactose monohydrate, see section 4.4.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light red, round tablets 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.

### 4.2 Posology and method of administration

#### Posology

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.

Xarelto can be taken with or without food.

#### Renal impairment

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). Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased in this patient population, 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).

#### Hepatic impairment

Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see sections 4.3 and 5.2). Xarelto may be used with caution in cirrhotic patients

with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (see sections 4.4 and 5.2).

No dose adjustment is necessary in patients with other hepatic diseases.

#### Elderly population

No dose adjustment.

#### Body weight

No dose adjustment.

#### Gender

No dose adjustment.

#### Paediatric population

The safety and efficacy of Xarelto in children 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

For oral use.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2).

Pregnancy and lactation (see section 4.6).

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

#### Haemorrhagic risk

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. 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.

#### Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. 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 sections 4.2 and 5.2).

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

#### Hepatic impairment

In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (see sections 4.2, 4.3 and 5.2).

### *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 which may lead to an increased bleeding risk (see section 4.5).

Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.

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

### *Other haemorrhagic risk factors*

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery.

### Hip fracture surgery

Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, rivaroxaban is not recommended in these patients.

### 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.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

### Interaction with CYP3A4 inducers

The concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution (see section 4.5).

### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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 [od]) or ritonavir (600 mg twice a day [bid]) 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). Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.

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 bid), for instance, considered as 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  $C_{max}$ . This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day [tid]), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and  $C_{max}$ . This increase is not considered clinically relevant.

### 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 section 4.4).

### NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban 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 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).

### 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) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

### 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) or atorvastatin (substrate of CYP3A4 and P-gp). 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 breast feeding**

#### 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).

#### Pregnancy

There are no adequate data from the use of rivaroxaban 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

No data on the use of rivaroxaban in breast feeding women are available. 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.

### **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 and dizziness have been reported to be common (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 10 mg has been evaluated in four phase III studies (RECORD 1-4) including 6,097 patients exposed to rivaroxaban undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated for up to 39 days.

In total, about 14 % of the treated patients experienced adverse reactions. Bleedings or anaemia occurred in approximately 3.3 % and 1 % of patients, respectively. Other common adverse reactions were nausea, increased GGT and an increase in transaminases. The adverse reactions should be interpreted within the surgical setting.

#### Tabulated summary of adverse reactions

The frequencies of adverse reactions reported with Xarelto in the phase III studies in patients undergoing elective hip or knee replacement surgery are summarized in table 1 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

Common:  $\geq 1/100$  to  $< 1/10$

Uncommon:  $\geq 1/1,000$  to  $< 1/100$

Rare:  $\geq 1/10,000$  to  $< 1/1,000$

Not known: cannot be estimated from the available data.

**Table 1: Treatment-emergent adverse reactions**

Common	Uncommon	Rare	Not known*
<b>Blood and lymphatic system disorders</b>			
	Anaemia (incl. respective laboratory parameter), thrombocythaemia (incl. platelet count increased)		
<b>Immune system disorders</b>			
		Dermatitis allergic	Hypersensitivity
<b>Nervous system disorders</b>			
	Dizziness, headache	Syncope (incl. loss of consciousness)	
<b>Cardiac disorders</b>			
	Tachycardia		
<b>Vascular disorders</b>			
Post-procedural haemorrhage (incl. post-operative anaemia, and wound haemorrhage)	Haematoma (incl. rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haememesis), urogenital tract haemorrhage, hypotension (incl. blood pressure decreased, procedural hypotension), nose bleed		Bleeding into a critical organ (e.g. brain), adrenal haemorrhage, conjunctival haemorrhage, haemoptysis, pseudoaneurysm formation following percutaneous intervention**
<b>Gastrointestinal disorders</b>			
Nausea	Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting		
<b>Hepatobiliary disorders</b>			
		Hepatic function abnormal	Jaundice
<b>Skin and subcutaneous tissue disorders</b>			
	Pruritus (incl. rare cases of generalised pruritus), rash, contusion	Urticaria (incl. rare cases of generalised urticaria)	
<b>Musculoskeletal and connective tissue disorders</b>			
	Pain in extremity		Compartment syndrome secondary to a bleeding
<b>Renal and urinary disorders</b>			
	Renal impairment (incl. blood creatinine increased, blood urea increased)		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion

Common	Uncommon	Rare	Not known*
<b>General disorders and administration site conditions</b>			
Fever, peripheral oedema	Localised oedema, decreased general strength and energy (incl. fatigue, asthenia)	Feeling unwell (incl. malaise)	
<b>Investigations</b>			
Increased GGT, increase in transaminases (incl. ALT increase, AST increase)	Increased lipase, increased amylase, blood bilirubin increased, increased LDH, increased alkaline phosphatase	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
<b>Injury, poisoning and procedural complications</b>			
	Wound secretion		

\*) Adverse events have been reported in other clinical studies than the four phase III studies in patients undergoing major orthopaedic surgery of the lower limbs or during postmarketing surveillance, for which a frequency could not be estimated

\*\*\*) These events occurred in clinical studies in other indications than prevention of VTE in patients undergoing major orthopaedic surgery

#### 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 posthaemorrhagic anaemia. The signs, symptoms, and severity (including possibly fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. 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 with other medicinal products affecting haemostasis (see Haemorrhagic risk in section 4.4).

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 may occur. Furthermore, known complications secondary to bleeding, such as compartment syndrome or renal failure might occur. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

## 4.9 Overdose

Overdose following administration of rivaroxaban may lead to haemorrhagic complications due to its pharmacodynamic properties.

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.

Should bleeding occur, management of the haemorrhage may include the following steps:

- delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has mean terminal half-lives between 7 and 11 hours (see section 5.2).
- appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.

If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving rivaroxaban. The recommendation is based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid, aminocaproic acid) 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: Other antithrombotic agents, ATC code: B01AX06

#### 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 (International Normalized Ratio) 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 15s).

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. Anti-Factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine.

#### Clinical efficacy and safety

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 2), 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 2: Efficacy and safety results from phase III clinical studies**

	RECORD 1			RECORD 2			RECORD 3		
Study Population	4,541 patients undergoing total hip replacement surgery			2,509 patients undergoing total hip replacement surgery			2,531 patients undergoing total knee replacement surgery		
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 trials 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.

#### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. 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 absolute bioavailability of rivaroxaban is high (80 % - 100 %) for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations ( $C_{max}$ ) appearing 2 - 4 hours after tablet intake. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 10 mg dose. Rivaroxaban 10 mg dose 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 the day of surgery and the following day when variability in exposure is high (70 %).

#### 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.

#### Metabolism 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 drug. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration of a 10 mg dose the elimination becomes absorption rate limited with mean terminal half-lives of 7 to 11 hours.

### 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. Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (see sections 4.3 and 4.4).

#### *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 bid). Rivaroxaban 10 mg od results in a steady state  $C_{max}$  of about 125 µg/l. 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 µg/l). The results of the PK/PD analyses in Phase II 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.

### **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 and genotoxicity.

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 and 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  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat:

Macrogol 3350  
Hypromellose  
Titanium dioxide (E171)  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

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

This medicinal product does not require any special storage conditions.

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

PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters in cartons of 5, 10 or 30 tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 tablets.  
Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer Pharma AG  
13342 Berlin  
Germany

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

EU/1/08/472/001-010

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

30 September 2008

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

{MM/YYYY}

Detailed information on this 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(s):

Each 15 mg film-coated tablet contains 25.4 mg lactose monohydrate, see section 4.4.

For a 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

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 prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

### 4.2 Posology and method of administration

#### Posology

#### Prevention of stroke and systemic embolism

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 and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT 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, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1 - 21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

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 (day 22 and onwards), 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 prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is  $\leq 3.0$ .

For patients treated for DVT and prevention of recurrent DVT and PE, 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 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, Xarelto should be started 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

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

#### Special populations

##### *Renal impairment*

No dose adjustment 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 the following dosage 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 and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

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).

#### *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 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

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

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Clinically significant active bleeding.

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

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia 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, 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.

#### 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 that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

#### 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, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

#### Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

#### 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 after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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  $C_{max}$ . This increase is not considered clinically relevant.

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  $C_{max}$ . This increase is not considered clinically relevant.

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  $C_{max}$ . This increase is not considered clinically relevant.

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 section 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).

#### 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) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

#### 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 breast feeding**

#### 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 and dizziness have been reported to be common (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 eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	Maximum 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
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

\*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

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

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

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

Not known: cannot be estimated from the available data.

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (VTE-P), treatment of DVT and prevention of recurrent DVT and PE (DVT-T), and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF))**

Common	Uncommon	Rare	Not known
<b>Blood and lymphatic system disorders</b>			
Anaemia (incl. respective laboratory parameters)	Thrombocytopenia (incl. platelet count increased) <sup>A</sup>		
<b>Immune system disorders</b>			
	Allergic reaction, dermatitis allergic		
<b>Nervous system disorders</b>			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		

Common	Uncommon	Rare	Not known
<b>Eye disorders</b>			
Eye haemorrhage (incl. conjunctival haemorrhage)			
<b>Cardiac disorders</b>			
Tachycardia			
<b>Vascular disorders</b>			
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	Haemoptysis		
<b>Gastrointestinal disorders</b>			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth		
<b>Hepatobiliary disorders</b>			
	Hepatic function abnormal	Jaundice	
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
<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) <sup>A</sup>		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>			

Common	Uncommon	Rare	Not known
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup> , increased GGT <sup>A</sup>	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
<b>Injury, poisoning and procedural complications</b>			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion	Wound secretion <sup>A</sup>		

A: observed in VTE-P; B: observed in DVT-T as very common in women < 55 years

\*) These reactions occurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

#### 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) and anemia 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, 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 Haemorrhagic risk in section 4.4). 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.

#### **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 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.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) 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: Other antithrombotic agents, ATC code: B01AX06

#### 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 (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, 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 16 to 33 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 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 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.

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. Anti-Factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine however, if clinically indicated haemostatic status can be assessed by testing as described above.

#### Clinical efficacy and safety

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

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto 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 Xarelto 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.

Xarelto 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 3.

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 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 4).

**Table 3: Efficacy results from phase III ROCKET AF**

•	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment)  Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)  Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value, test for superiority
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 infaction	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 infaction	130 (1.02%)	142 (1.11%)	0.91 (0.72 - 1.16) 0.464

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

• Study population	• Patients with non-valvular atrial fibrillation <sup>a</sup>		
Treatment dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment)  Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)  Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value
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

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

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall combined treatment duration in both 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.

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. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies 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 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: 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 hazard ratio 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 - 3) 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 hazard ratio 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.

In the Einstein Extension study (see Table 6) 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.

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 -- 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e. 15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

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

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto <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 followed by VKA

\*  $p < 0.0001$  (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

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

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto <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), hazard ratio: 0.185 (0.087 - 0.393)

### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. 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 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 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 Xarelto 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. Xarelto 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 Xarelto 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%.

### 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 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) µg/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 µg/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 reproductive 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  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat:

Macrogol 3350  
Hypromellose  
Titanium dioxide (E171)  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

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

This medicinal product does not require any special storage conditions.

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

PP/Aluminium foil blisters in cartons of 14, 28, 42 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer Pharma AG  
13342 Berlin  
Germany

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

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

30 September 2008

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

{MM/YYYY}

Detailed information on this 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(s):

Each 20 mg film-coated tablet contains 22.9 mg lactose monohydrate, see section 4.4.

For a 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

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 prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

### 4.2 Posology and method of administration

#### Posology

#### Prevention of stroke and systemic embolism

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 and prevention of recurrent DVT and PE

The recommended dose for the initial treatment of acute DVT 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, as indicated in the table below.

	Dosing schedule	Maximum daily dose
Day 1-21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). Short duration of therapy (3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT. Experience with Xarelto in this indication for more than 12 months is limited.

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 (day 22 and onwards), 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 prevention of stroke and systemic embolism, VKA treatment should be stopped and Xarelto therapy should be initiated when the INR is  $\leq 3.0$ .

For patients treated for DVT and prevention of recurrent DVT and PE, 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 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, Xarelto should be started 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

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

#### Special populations

##### *Renal impairment*

No dose adjustment 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 the following dosage 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 and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, the recommended dose is 15 mg once daily based on PK modelling (see sections 4.4 and 5.2).

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).

#### *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 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

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

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Clinically significant active bleeding.

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

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia 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, 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.

#### 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 that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.

#### 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, platelet aggregation inhibitors or other antithrombotic agents. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

#### Other haemorrhagic risk factors

Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- recent gastrointestinal ulcerations
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- recent brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

#### Patients with prosthetic valves

Safety and efficacy of Xarelto have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Xarelto 20 mg (15 mg in patients with moderate or severe renal impairment) provides adequate anticoagulation in this patient population. Treatment with Xarelto is not recommended for these patients.

#### Patients with acute pulmonary embolism

Xarelto is not recommended in the treatment of acute pulmonary embolism.

#### 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 after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

#### Information about excipients

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp 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  $C_{max}$ . This increase is not considered clinically relevant.

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  $C_{max}$ . This increase is not considered clinically relevant.

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  $C_{max}$ . This increase is not considered clinically relevant.

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 section 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).

#### 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) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

#### 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 breast feeding**

#### 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 and dizziness have been reported to be common (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 eight phase III studies including 16,041 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	Maximum 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
Treatment of DVT and prevention of recurrent DVT and PE	2,194	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

\*Patients exposed to at least one dose of rivaroxaban

In total about 73% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 24% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xarelto undergoing hip or knee replacement surgery, bleeding events occurred in approximately 6.8% of patients and anaemia occurred in approximately 5.9% of patients. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 22.7% of patients and anaemia occurred in approximately 1.8% of patients. In patients treated for prevention of stroke and systemic embolism, bleeding of any type or severity was reported with an event rate of 28 per 100 patient years, and anaemia with an event rate of 2.5 per 100 patient years.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:

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

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

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

Not known: cannot be estimated from the available data.

**Table 2: All treatment-emergent adverse reactions reported in patients in phase III studies (prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery (VTE-P), treatment of DVT and prevention of recurrent DVT and PE (DVT-T), and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF))**

Common	Uncommon	Rare	Not known
<b>Blood and lymphatic system disorders</b>			
Anaemia (incl. respective laboratory parameters)	Thrombocytopenia (incl. platelet count increased) <sup>A</sup>		
<b>Immune system disorders</b>			
	Allergic reaction, dermatitis allergic		
<b>Nervous system disorders</b>			
Dizziness, headache, syncope	Cerebral and intracranial haemorrhage		

Common	Uncommon	Rare	Not known
<b>Eye disorders</b>			
Eye haemorrhage (incl. conjunctival haemorrhage)			
<b>Cardiac disorders</b>			
Tachycardia			
<b>Vascular disorders</b>			
Hypotension, haematoma			Pseudoaneurysm formation following percutaneous intervention*
<b>Respiratory, thoracic and mediastinal disorders</b>			
Epistaxis	Haemoptysis		
<b>Gastrointestinal disorders</b>			
Gastrointestinal tract haemorrhage (incl. gingival bleeding and rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation <sup>A</sup> , diarrhoea, vomiting <sup>A</sup>	Dry mouth		
<b>Hepatobiliary disorders</b>			
	Hepatic function abnormal	Jaundice	
<b>Skin and subcutaneous tissue disorders</b>			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis	Urticaria, cutaneous and subcutaneous haemorrhage		
<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) <sup>A</sup>		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>			

Common	Uncommon	Rare	Not known
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase <sup>A</sup> , increased LDH <sup>A</sup> , increased lipase <sup>A</sup> , increased amylase <sup>A</sup> , increased GGT <sup>A</sup>	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
<b>Injury, poisoning and procedural complications</b>			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion	Wound secretion <sup>A</sup>		

A: observed in VTE-P; B: observed in DVT-T as very common in women < 55 years

\*) These reactions occurred in other clinical studies than the phase III studies in patients undergoing major orthopaedic surgery of the lower limbs, patients treated for DVT and prevention of recurrent DVT and PE, or patients treated for the prevention of stroke and systemic embolism

#### 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) and anemia 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, 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 Haemorrhagic risk in section 4.4). 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.

#### **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 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.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) 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: Other antithrombotic agents, ATC code: B01AX06

#### 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 (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of DVT and prevention of recurrent DVT and PE, 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 16 to 33 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 25 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 21 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.

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. Anti-Factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine however, if clinically indicated haemostatic status can be assessed by testing as described above.

## Clinical efficacy and safety

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

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto 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 Xarelto 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.

Xarelto 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 3.

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 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 4).

**Table 3: Efficacy results from phase III ROCKET AF**

•	• ITT analyses of efficacy in patients with non-valvular atrial fibrillation		
Treatment, dosage	Xarelto 20 mg od (15 mg od in patients with moderate renal impairment)  Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)  Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value, test for superiority
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 infaction	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 infaction	130 (1.02%)	142 (1.11%)	0.91 (0.72 - 1.16) 0.464

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

• Study population	• Patients with non-valvular atrial fibrillation <sup>a</sup>		
Treatment, dosage	Xarelto 20 mg once a day (15 mg once a day in patients with moderate renal impairment)  Event rate (100 pt-yr)	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)  Event rate (100 pt-yr)	Hazard ratio (95% CI) p-value
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

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

The Xarelto clinical program was designed to demonstrate the efficacy of Xarelto in the initial and continued treatment of acute DVT and prevention of recurrent DVT and PE.

Over 4,600 patients were studied in two randomised controlled phase III clinical studies (Einstein DVT and Einstein Extension). The overall combined treatment duration in both 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.

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. Xarelto 20 mg once daily was compared with placebo.

Both phase III studies 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 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: 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 hazard ratio 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 - 3) 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 hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI, 0.35 to 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.

In the Einstein Extension study (see Table 6) 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.

In both the Einstein DVT and Einstein Extension studies, patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) were treated with the same dose as patients with creatinine clearance above 50 ml/min (i.e. 15 mg twice daily for the first three weeks and 20 mg once daily from day 22 onwards).

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

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment dosage and duration	Xarelto <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 followed by VKA

\*  $p < 0.0001$  (non-inferiority); hazard ratio: 0.680 (0.443 - 1.042),  $p=0.076$  (superiority)

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

Study Population	1,197 patients continued treatment and prevention of recurrent venous thromboembolism	
Treatment dosage and duration	Xarelto <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), hazard ratio: 0.185 (0.087 - 0.393)

### Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xarelto in one or more subsets of the paediatric population in the treatment of thromboembolic events. 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 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 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 Xarelto 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. Xarelto 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 Xarelto 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%.

### 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 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) µg/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 µg/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 reproductive 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  
Sodium laurilsulfate  
Magnesium stearate

#### Film-coat:

Macrogol 3350  
Hypromellose  
Titanium dioxide (E171)  
Iron oxide red (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years

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

This medicinal product does not require any special storage conditions.

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

PP/Aluminium foil blisters in cartons of 14, 28 or 98 film-coated tablets or perforated unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Bayer Pharma AG  
13342 Berlin  
Germany

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

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

30 September 2008

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

{MM/YYYY}

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

## **ANNEX II**

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

## **A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

### Name and address of the manufacturer responsible for batch release

Bayer Pharma AG  
51368 Leverkusen  
Germany

### Additionally for 10 mg film-coated tablets only

Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy

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**

### Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

### Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

### PSURs

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Xarelto, prior to the launch of the new indication for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Xarelto, prior to the launch of the new indication for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

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 MAH must agree the content and format of the educational material, 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 physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

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 provided with a Patient alert card and 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 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.

The Patient alert card should contain the following key safety messages:

- 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 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.

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Outer Carton**

**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 leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

5 film-coated tablets  
10 film-coated tablets  
30 film-coated tablets  
10 x 1 film-coated tablets  
100 x 1 film-coated tablets

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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 Pharma AG,  
13342 Berlin,  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

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)

**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

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 10 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 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 leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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**

For oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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 Pharma AG  
13342 Berlin  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**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

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Unit dose blister (10 x 1 tablets) for 15 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 mg tablets  
Rivaroxaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Bayer (logo)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister of 14 tablets for 15 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 15 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

**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 leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

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**

For oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight 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 Pharma AG  
13342 Berlin  
Germany

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/0/00/000/000

**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

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Unit dose blister (10 x 1 tablets) for 20 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 mg tablets  
Rivaroxaban

**2. NAME OF THE MARKETING AUTHORISATION HOLDER**

Bayer (logo)

**3. EXPIRY DATE**

EXP

**4. BATCH NUMBER**

Lot

**5. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**Blister of 14 tablets for 20 mg**

**1. NAME OF THE MEDICINAL PRODUCT**

Xarelto 20 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

**B. PACKAGE LEAFLET**

## 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.**

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What Xarelto is and what it is used for
2. Before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Further information

### **1. WHAT XARELTO IS AND WHAT IT IS USED FOR**

Xarelto is used to prevent blood clots in your 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.

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. BEFORE YOU TAKE XARELTO**

#### **Do not take Xarelto**

- **if you are allergic** (hypersensitive) to rivaroxaban or any of the other ingredients of Xarelto. The ingredients are listed at the end of this leaflet
- **if you are bleeding excessively**
- **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.

#### **Take special care with Xarelto**

- if you have **moderate or severe kidney disease**
- if you have **moderate liver disease**
- if you have **an increased risk of bleeding** such as:
  - **bleeding disorders**
  - **very high blood pressure**, not controlled by medical treatment
  - **active ulcer or a recent ulcer** of your stomach or bowel
  - **a problem with the blood vessels in the back of your eyes** (retinopathy)
  - **recent bleeding in your brain** (intracranial or intracerebral bleeding)
  - **problems with the blood vessels in your brain or spinal column**
  - **a recent operation on your brain, spinal column or eye**

**Tell your doctor** before you take Xarelto, if any of these apply to you. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

- Xarelto is **not recommended after an operation of a hip fracture.**
- **in children and adolescents**, Xarelto is **not recommended for people under 18 years of age.** There is not enough information on its use in children and adolescents.
- **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.

### **Taking other medicines**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

- **If you are taking:**
  - some **medicines for fungal infections** (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole), unless they are only applied to the skin
  - some **anti-viral medicines for HIV / AIDS** (e.g. ritonavir)
  - other medicines to **reduce blood clotting** (e.g. enoxaparin or clopidogrel)
  - **anti-inflammatory and pain relieving medicines** (e.g. naproxen or acetylsalicylic acid)

**Tell your doctor** before taking Xarelto, because its effect may be increased. Your doctor will decide, if you should be treated with Xarelto 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 Johns Wort**, a herbal product used for depression,
  - **rifampicin**, an antibiotic.

**Tell your doctor** before taking Xarelto, because its effect may be reduced. Your doctor will decide, if you should be treated with Xarelto and if you should be kept under closer observation.

### **Taking Xarelto with food and drink**

Xarelto can be taken with or without food.

### **Pregnancy and breast feeding**

**If you are pregnant or breast feeding** do not take Xarelto. 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 Xarelto, immediately tell your doctor, who will decide how you should be treated.

### **Driving and using machines**

Xarelto may cause side effects such as dizziness or fainting. You should not drive or use machines if you are affected by these symptoms. For Xarelto, these side effects are uncommon (see section 4 “Possible side effects”).

### **Important information about some of the ingredients of Xarelto**

**Xarelto contains lactose.** If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Xarelto.

## **3. HOW TO TAKE XARELTO**

Always take Xarelto exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

### **How much to take**

**The usual dose is one tablet (10 mg) once a day.**

Swallow the tablet preferably with water.  
Xarelto can be taken with or without food.

#### **When to take Xarelto**

##### **Take the first tablet 6 - 10 hours after your operation.**

Then take a 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.

**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**

Don't 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 product, 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 (antithrombotic agents), Xarelto may cause bleedings which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases these bleedings may not be obvious.

**Tell your doctor**, if you experience any of the following side effects:

- **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 how you should be treated.

The frequency of possible side effects listed below is defined using the following convention:

common (affects 1 to 10 users in 100)

uncommon (affects 1 to 10 users in 1,000)

rare (affects 1 to 10 users in 10,000)

not known (frequency cannot be estimated from the available data).

#### **Common side effects**

- bleeding following your operation
- feeling sick, fever, swelling in your limbs
- blood tests may show an increase in some liver enzymes

#### **Uncommon side effects**

- bleeding in your stomach or bowel, urogenital bleeding, nose bleed
- bleeding into tissue or a cavity of your body (haematoma, bruising)
- oozing of blood or fluid from surgical wound
- raised heartbeat
- low blood pressure
- decreased general strength and energy (weakness, tiredness), headache, dizziness

- reduction in red blood cells which can make your skin pale and cause weakness or breathlessness
- stomach ache, indigestion, constipation, diarrhoea, being sick
- dry mouth
- localised swelling
- pain in your limbs
- rash, itchy skin
- impaired function of your kidneys
- blood tests may show an increase in bilirubin, some pancreatic enzymes or in the number of platelets

#### **Rare side effects**

- impaired function of your liver
- allergic skin reactions, hives
- fainting, feeling unwell

#### **Side effects where frequency is not known**

- bleeding into a critical organ (e.g. your brain)
- adrenal bleeding
- bleeding from the whites of your eyes
- collection of blood (haematoma) following complication in a cardiac procedure where a catheter is inserted to treat narrowed coronary arteries (pseudoaneurysm)
- coughing up blood
- increased pressure within muscles of your legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)
- kidney failure after a severe bleeding
- yellowing of the skin and eye (jaundice)
- hypersensitivity

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

## **5. HOW TO STORE XARELTO**

Keep out of the reach and sight of children.

Do not use Xarelto after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER 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, sodium laurilsulfate, magnesium stearate.  
Film coat: macrogol 3350, hypromellose, titanium dioxide (E171), iron oxide red (E172).

**What Xarelto looks like and contents of the pack**

The film-coated tablets are light red, round 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 or 30 tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 tablets.

Not all pack-sizes may be marketed.

**Marketing Authorisation Holder**

Bayer Pharma AG  
13342 Berlin  
Germany

**Manufacturer**

Bayer Pharma AG  
51368 Leverkusen  
Germany

and

Bayer HealthCare Manufacturing Srl.  
Via delle Groane, 126  
20024 Garbagnate Milanese  
Italy

For more 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)2-81 401 01

**Česká republika**

Bayer s.r.o.

Tel: +420-266 101 111

**Danmark**

Bayer A/S

Tlf: +45-45 235 000

**Deutschland**

Bayer Vital GmbH

Tel: +49-(0)214-30 513 48

**Eesti**

Bayer OÜ

Tel: +372-655 85 65

**Ελλάδα**

Bayer Ελλάς ABEE

Τηλ: +30-210-618 75 00

**España**

Bayer Hispania S.L.

Tel: +34-93-495 65 00

**France**

Bayer Santé

Tél: +33-(0)3-28 16 34 00

**Ireland**

Bayer Limited

Tel: +353-(0)1-2999 313

**Ísland**

Icepharma hf.

Sími: +354-540 80 00

**Italia**

Bayer S.p.A.

Tel: +39-02-3978 1

**Κύπρος**

NOVAGEM Limited

Τηλ: +357-22-747 747

**Latvija**

SIA Bayer

Tel: +371-67 84 55 63

**Lietuva**

UAB Bayer

Tel: +370-5-233 68 68

**Luxembourg / Luxemburg**

Bayer SA-NV

Tél/Tel: +32-(0)2-535 63 11

**Magyarország**

Bayer Hungária KFT

Tel: +36-1-487 4100

**Malta**

Alfred Gera and Sons Ltd.

Tel: +356-21 44 62 05

**Nederland**

Bayer B.V.

Tel: +31-(0)297-28 06 66

**Norge**

Bayer AS

Tlf: +47-24 11 18 00

**Österreich**

Bayer Austria Ges. m. b. H.

Tel: +43-(0)1-711 460

**Polska**

Bayer Sp. z o.o.

Tel: +48-22-572 35 00

**Portugal**

Bayer Portugal S.A

Tel: +351-21-416 42 00

**România**

SC Bayer SRL

Tel: +40-(0)21-528 59 00

**Slovenija**

Bayer d. o. o.

Tel: +386-(0)1-58 14 400

**Slovenská republika**

Bayer, spol. s r.o.

Tel: +421-(0)2-59 21 31 11

**Suomi/Finland**

Bayer Oy

Puh/Tel: +358-(0)20-78521

**Sverige**

Bayer AB

Tel: +46-(0)8-580 223 00

**United Kingdom**

Bayer plc

Tel: +44-(0)1635-563000

**This leaflet was last approved in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<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.**

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What Xarelto is and what it is used for
2. Before you take Xarelto
3. How to take Xarelto
4. Possible side effects
5. How to store Xarelto
6. Further information

### **1. WHAT XARELTO IS AND WHAT IT IS USED FOR**

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 to **prevent blood clots** from re-occurring in the veins of your legs and/or lungs (*pulmonary embolism*).

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. BEFORE YOU TAKE XARELTO**

**Do not take Xarelto**

- **if you are allergic (*hypersensitive*)** to rivaroxaban or any of the other ingredients of Xarelto (listed in section 6 of this leaflet)
- **if you are bleeding excessively**
- **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.

### 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**
  - **bleeding disorders**
  - **very high blood pressure**, not controlled by medical treatment
  - **active ulcer or a recent ulcer** of your stomach or bowel
  - **a problem with the blood vessels in the back of your eyes** (*retinopathy*)
  - **recent bleeding in your brain** (*intracranial or intracerebral bleeding*)
  - **problems with the blood vessels in your brain or spinal column**
  - **a recent operation on your brain, spinal column or eye**
  - **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 have **blood clots in the veins of your lungs**

**Tell your doctor** before you take Xarelto, if any of these apply to you. Your doctor will decide, if you should be treated with Xarelto 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.

### Children and adolescents

Xarelto is **not recommended for people under 18 years of age**.

### Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

- **If you are taking:**
  - some **medicines for fungal infections** (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
  - some **anti-viral medicines for HIV / AIDS** (e.g. ritonavir)
  - other medicines to **reduce blood clotting** (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
  - **anti-inflammatory and pain relieving medicines** (e.g. naproxen or acetylsalicylic acid)

**Tell your doctor** before taking Xarelto, because the effect of Xarelto may be increased. Your doctor will decide, if you should be treated with Xarelto 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**, a herbal product used for depression
  - **rifampicin**, an antibiotic

**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

**If you are pregnant or breast feeding** do not take Xarelto. 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 Xarelto, immediately tell your doctor, who will decide how you should be treated.

### Driving and using machines

Xarelto may cause side effects such as dizziness or fainting (see section 4, 'Possible side effects'). These side effects are common. You should not drive or use machines if you are affected by these symptoms.

### **Important information about some of the ingredients of Xarelto**

Xarelto contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Xarelto.

### **3. HOW TO TAKE XARELTO**

Always take Xarelto exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

#### **How much to take**

- **To prevent blood clots in brain (*stroke*) and other blood vessels in your body**  
The usual dose is one 20 mg tablet once a day.  
**If you have kidney problems**, the dose may be reduced to one 15 mg tablet once a day.
  
- **To treat blood clots in the veins of your legs and for preventing blood clots from re-occurring**  
The usual dose is one 15 mg tablet twice a day for the first 3 weeks. For treatment after 3 weeks, the usual dose is one 20 mg tablet once a day.  
**If you have kidney problems**, the usual dose is one 15 mg tablet twice a day for the first 3 weeks. For treatment after 3 weeks, the dose may be reduced from one 20 mg tablet once a day to one 15 mg tablet once a day.

Swallow the tablet(s) preferably with water.

Take Xarelto together with a meal.

#### **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 for.

#### **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 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.
  
- **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 stop taking Xarelto**

Don't 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 (*antithrombotic agents*), 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.

Possible side effects which may be a sign of bleeding:

**Tell your doctor immediately** if you experience any of the following side effects:

- **long or excessive bleeding**
- **exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris**, which may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

Overall list of possible side effects:

##### **Common side effects**

*(affect 1 to 10 users in 100)*

- 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)
- bleeding following an operation
- swelling in the limbs
- pain in the limbs
- fever
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- raised heartbeat
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness, fainting
- rash, itchy skin
- blood tests may show an increase in some liver enzymes

##### **Uncommon side effects**

*(affect 1 to 10 users in 1,000)*

- bleeding into the brain or inside the skull
- bleeding into a joint causing pain and swelling
- coughing up blood
- bleeding from the skin or under the skin
- oozing of blood or fluid from surgical wound
- feeling unwell
- dry mouth
- localised swelling
- allergic reactions, including allergic skin reactions
- hives
- impaired function of the kidneys or 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

##### **Rare side effects**

*(affect 1 to 10 users in 10,000)*

- bleeding into a muscle
- yellowing of the skin and eye (*jaundice*)

### **Side effects where frequency is not known**

*(frequency cannot be estimated from the available data)*

- collection of blood (*haematoma*) following complication in a cardiac procedure where a catheter is inserted to treat narrowed coronary arteries (*pseudoaneurysm*)
- 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*)
- kidney failure after a severe bleeding

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

## **5. HOW TO STORE XARELTO**

Keep out of the reach and sight of children.

Do not use Xarelto after the expiry date which is stated on the carton and on each blister after EXP. The expiry date refers to the last day of the month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **6. FURTHER 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, sodium laurilsulfate, magnesium stearate.
  - Film coat: macrogol 3350, hypromellose, titanium dioxide (E171), iron oxide red (E172).

### **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 14, 28, 42 or 98 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 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 14, 28 or 98 film-coated tablets or unit dose blisters in cartons of 10 x 1 or 100 x 1 film-coated tablets.

Not all pack sizes may be marketed.

### **Marketing Authorisation Holder**

Bayer Pharma AG  
13342 Berlin  
Germany

**Manufacturer**

Bayer Pharma 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  
Тел: +359-(0)2-81 401 01

**Česká republika**

Bayer s.r.o.  
Tel: +420-266 101 111

**Danmark**

Bayer A/S  
Tlf: +45-45 235 000

**Deutschland**

Bayer Vital GmbH  
Tel: +49-(0)214-30 513 48

**Eesti**

Bayer OÜ  
Tel: +372-655 85 65

**Ελλάδα**

Bayer Ελλάς ABEE  
Τηλ: +30-210-618 75 00

**España**

Bayer Hispania S.L.  
Tel: +34-93-495 65 00

**France**

Bayer Santé  
Tél: +33-(0)3-28 16 34 00

**Ireland**

Bayer Limited  
Tel: +353-(0)1-2999 313

**Ísland**

Icepharma hf.  
Sími: +354-540 80 00

**Italia**

Bayer S.p.A.  
Tel: +39-02-3978 1

**Κύπρος**

NOVAGEM Limited  
Τηλ: +357-22-48 38 58

**Latvija**

SIA Bayer  
Tel: +371-67 84 55 63

**Lietuva**

UAB Bayer  
Tel: +370-5-233 68 68

**Luxembourg / Luxemburg**

Bayer SA-NV  
Tél/Tel: +32-(0)2-535 63 11

**Magyarország**

Bayer Hungária KFT  
Tel: +36-1-487 4100

**Malta**

Alfred Gera and Sons Ltd.  
Tel: +356-21 44 62 05

**Nederland**

Bayer B.V.  
Tel: +31-(0)297-28 06 66

**Norge**

Bayer AS  
Tlf: +47-24 11 18 00

**Österreich**

Bayer Austria Ges. m. b. H.  
Tel: +43-(0)1-711 460

**Polska**

Bayer Sp. z o.o.  
Tel: +48-22-572 35 00

**Portugal**

Bayer Portugal S.A  
Tel: +351-21-416 42 00

**România**

SC Bayer SRL  
Tel: +40-(0)21-528 59 00

**Slovenija**

Bayer d. o. o.  
Tel: +386-(0)1-58 14 400

**Slovenská republika**

Bayer, spol. s r.o.  
Tel: +421-(0)2-59 21 31 11

**Suomi/Finland**

Bayer Oy  
Puh/Tel: +358-(0)20-78521

**Sverige**

Bayer AB  
Tel: +46-(0)8-580 223 00

**United Kingdom**

Bayer plc  
Tel: +44-(0)1635-563000

**This leaflet was last approved in {MM/YYYY}**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>