

Summary of Product Characteristics – EU





1. Name of the medicinal product

Xarelto 10 mg film-coated tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 10 mg rivaroxaban.

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

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.

PATIENTS ABOVE 65 YEARS

No dose adjustment.

BODY WEIGHT

No dose adjustment.

GENDER

No dose adjustment.

CHILDREN AND ADOLESCENTS

Xarelto is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

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-anti-mycotics (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 a smaller 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 (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 (eg, 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 Pregnancy and lactation

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.

LACTATION

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

No studies of the effects on the ability to drive and use machines have been performed.

Syncope and dizziness have been reported in the post-operative setting and may affect the ability to drive and use machines, these adverse reactions have been reported to be uncommon (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

The safety of rivaroxaban 10 mg has been evaluated in three phase III studies including 4,571 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.

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. 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, asthenia, paleness, dizziness, headache or unexplained swelling. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Adverse reactions in the three phase III studies are listed in table 1 below by system organ class (in MedDRA) and by frequency.

FREQUENCIES ARE DEFINED AS

Common:	≥1/100 to <1/10
Uncommon:	≥1/1,000 to <1/100
Rare:	≥1/10,000 to <1/1,000
Very rare:	<1/10,000
Not known:	cannot be estimated from the available data.



TABLE 1: TREATMENT-EMERGENT ADVERSE REACTIONS IN THREE PHASE III STUDIES

	Common	Uncommon	Rare	Not known*
Investigations	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)	
Cardiac disorders		Tachycardia		
Blood and lymphatic system disorders	Anaemia (incl. respective laboratory parameter)	Thrombocythaemia (incl. platelet count increased)		
Nervous system disorders		Syncope (incl. loss of consciousness), dizziness, headache		
Gastrointestinal disorders	Nausea	Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting		
Renal and urinary disorders		Renal impairment (incl. blood creatinine increased, blood urea increased)		
Skin and subcutaneous tissue disorders		Pruritus (incl. rare cases of generalised pruritus), rash, urticaria (incl. rare cases of generalised urticaria), contusion		
Musculoskeletal and connective tissue disorders		Pain in extremity		
Injury, poisoning and procedural complications		Wound secretion		
Vascular disorders	Post-procedural haemorrhage (incl. post-operative anaemia, and wound haemorrhage)	Haemorrhage (incl. haematoma and rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haememesis), haematuria (incl. blood urine present), genital tract haemorrhage (incl. menorrhagia), hypotension (incl. blood pressure decreased, procedural hypotension), nose bleed		Bleeding into a critical organ (e.g. brain), adrenal haemorrhage, conjunctival haemorrhage, haemoptysis
General disorders and administration site conditions		Localised oedema, peripheral oedema, feeling unwell (incl. fatigue, asthenia), fever		
Immune system disorders			Dermatitis allergic	Hypersensitivity
Hepatobiliary disorders			Hepatic function abnormal	Jaundice

*Adverse events have been reported in other clinical studies than the three phase III studies in patients undergoing major orthopaedic surgery of the lower limbs.



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 15 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.

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

STUDY	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 dosage 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 bleeding	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.

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. The 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/ELDERLY (ABOVE 65 YEARS)

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.

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

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 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.

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, 30, and 100 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. Marketing authorisation holder

Bayer HealthCare AG, D-51368 Leverkusen, Germany

8. Marketing authorisation number(s)

EU/1/08/472/001, EU/1/08/472/002, EU/1/08/472/003, EU/1/08/472/004, EU/1/08/472/005, EU/1/08/472/006, EU/1/08/472/007, EU/1/08/472/008

9. Date of first authorisation / Renewal of the authorisation

30/09/2008

10. Date of revision of the text

09/2008

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