

# DATASHEET

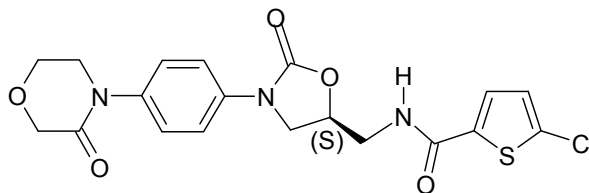
## XARELTO® (rivaroxaban)

### NAME OF THE MEDICINE

Xarelto (rivaroxaban) is a selective, direct acting Factor Xa inhibitor.

Rivaroxaban is 5-Chloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl)methyl)-2-thiophene-carboxamide. The empirical formula is C<sub>19</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>5</sub>S, molecular weight is 435.89 g/mole and CAS number is 366789-02-8.

Rivaroxaban has the following structural formula:



### DESCRIPTION

Rivaroxaban is an odourless, non-hygroscopic white to yellowish powder. Rivaroxaban is practically insoluble in water and aqueous media in the pH range 1 to 9. An amount of approximately 5 - 7 mg/L rivaroxaban is pH-independently soluble in aqueous media at 25 °C. Rivaroxaban is only slightly soluble in organic solvents (e.g. acetone, polyethylene glycol 400).

Each film-coated tablet contains 10 mg of rivaroxaban.

In addition, each Xarelto tablet contains:

*Tablet core:* Microcrystalline cellulose, croscarmellose sodium, lactose, hypromellose, sodium lauryl sulfate, magnesium stearate.

*Filmcoat:* Macrogol 3350, hypromellose, titanium dioxide, iron oxide red.

### PHARMACOLOGY

#### Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent

#### *Mechanism of Action*

Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability.

Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able

to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose-dependent inhibition of Factor Xa activity was observed in humans.

#### *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<sup>®</sup> is used for the assay. Other reagents would provide different results. The read-out for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for coumarins and can not be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin<sup>®</sup>) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 seconds.

The activated partial thromboplastin time (aPTT) and HepTest<sup>®</sup> 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 Xarelto.

No QTc prolonging effect was observed with rivaroxaban.

### **Pharmacokinetic properties**

#### *Absorption and Bioavailability*

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.

Xarelto 10 mg dose can be taken with or without food. Intake with food does not affect rivaroxaban AUC or  $C_{max}$  at the 10 mg dose. (see DOSAGE AND ADMINISTRATION).

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 human 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 L.

### *Metabolism and Elimination*

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

### *Gender/Elderly (above 65 years)*

Whilst 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 (see DOSAGE AND ADMINISTRATION).

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients (see DOSAGE AND ADMINISTRATION).

### *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 (see DOSAGE AND ADMINISTRATION).

### *Children and adolescents (from birth to 18 years)*

No data are available for this patient population (see DOSAGE AND ADMINISTRATION).

### *Interethnic differences*

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics (see DOSAGE AND ADMINISTRATION).

### *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. No relevant

difference in pharmacodynamic properties was observed between these groups. 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, due to significantly impaired drug clearance which indicates significant liver disease. The inhibition of FXa activity was increased by a factor of 2.6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1.

The global clotting test PT assesses the extrinsic pathway that comprises of coagulation Factors VII, X, V, II, and I, which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT. The elevated PT at baseline and a significantly altered sensitivity in anti-coagulant activity towards rivaroxaban plasma exposure (increase in slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients with moderate hepatic impairment indicate the decreased ability of the liver to synthesize coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group.

Therefore Xarelto is contraindicated in patients with hepatic disease (including moderate and severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. No data are available for severe hepatic impairment (Child Pugh C patients) (see DOSAGE AND ADMINISTRATION). Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment if it is not associated with coagulopathy.

#### *Renal impairment*

There was an increase in rivaroxaban exposure being inversely correlated to the decrease in renal function, as assessed via creatinine clearance (CrCl) 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 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).

Corresponding increases in pharmacodynamic effects were more pronounced (see DOSAGE AND ADMINISTRATION and PRECAUTIONS) in individuals with mild, moderate or severe renal impairment; the overall inhibition of FXa 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 CrCl < 15 mL/min. Use is contraindicated in patients with creatinine clearance < 15 mL/min (see CONTRAINDICATIONS). Xarelto is to be used with caution in patients with severe renal impairment creatinine clearance 15 - 29 mL/min (see DOSAGE AND ADMINISTRATION and PRECAUTIONS). Due to the underlying disease, patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. The increased exposure to rivaroxaban further increases the risk of bleeding in these patients. Due to the high plasma protein binding, rivaroxaban is not expected to be dialysable.

## CLINICAL STUDIES

### Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs

The rivaroxaban clinical program was designed to demonstrate the efficacy of Xarelto for the prevention of venous thromboembolic events (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, known as the RECORD-program.

RECORD 1 and 2 were conducted in patients undergoing elective total hip replacement surgery (THR) and RECORD 3 was performed in patients undergoing elective total knee replacement (TKR) surgery. Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery.

**Table 1** – Patient demographics

| Study          | No of patients                      | N (%) / Sex         |                        | Mean age $\pm$ SD (years) |
|----------------|-------------------------------------|---------------------|------------------------|---------------------------|
|                |                                     |                     |                        |                           |
| RECORD 1 (THR) | 2209 rivaroxaban<br>2224 enoxaparin | 1971(44.5)/<br>male | 2462 (55.5)/<br>female | 63.2 $\pm$ 11.4           |
| RECORD 2 (THR) | 1228 rivaroxaban<br>1229 enoxaparin | 1139 (46)/<br>male  | 1318 (54)/<br>female   | 61.5 $\pm$ 13.4           |
| RECORD 3 (TKR) | 1220 rivaroxaban<br>1239 enoxaparin | 781 (31.8)/<br>male | 1678 (68.2)/<br>female | 67.6 $\pm$ 9.0            |

The respective studies were heterogeneous with respect to their composition of participating countries (centres from Europe, North and South America, Asia and Australia). Men and women of 18 years or older scheduled for hip or knee replacement surgery could be enrolled provided that they had no active or high risk of bleeding or other conditions contraindicating treatment with low-molecular weight heparin, no significant liver disease, were not pregnant or breastfeeding, or were not using HIV protease inhibitors.

In all three pivotal studies, rivaroxaban 10 mg once-daily started not earlier than 6 hours postoperatively was compared with enoxaparin 40 mg once-daily started 12 hours preoperatively.

The primary efficacy analysis in all studies was based on stratified (by geographical region) risk difference between rivaroxaban and enoxaparin and corresponding 2-sided 95 % confidence intervals. Efficacy was assessed in two steps; first a non-inferiority test

was performed based on the per protocol population. Since non-inferiority was shown, a pre-specified superiority analysis was performed subsequently based on the modified ITT population.

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 or death) and major VTE (proximal DVT, non-fatal PE or VTE-related death), the pre-specified primary and major secondary efficacy endpoints. The results were clinically meaningful and statistically significant. Relative risk reductions in total VTE were 49 % (RECORD 3) and 70 % (RECORD 1) in comparison to enoxaparin and 79 % (RECORD 2) in comparison to enoxaparin/placebo. 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                            | 4541 patients undergoing total hip replacement surgery |   |         | 2509 patients undergoing total hip replacement surgery |   |         | 2531 patients undergoing total knee replacement surgery |   |         |
| Treatment dosage and duration after surgery | Rivaroxaban 10 mg o.d.<br>35 ± 4 days<br>n (%)         | Enoxaparin 40 mg o.d.<br>35 ± 4 days<br>n (%) | p-value | Rivaroxaban 10 mg o.d.<br>35 ± 4 days<br>n (%)         | Enoxaparin 40 mg o.d.<br>12 ± 2 days<br>n (%) | p-value | Rivaroxaban 10 mg o.d.<br>12 ± 2 days<br>n (%)          | Enoxaparin 40 mg o.d.<br>12 ± 2 days<br>n (%) | p-value |
| 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 %)                                     | --      |
| PE (non-fatal)                              | 4 (0.3 %)  | 1 (< 0.1 %)                                   | --      | 1 (0.1 %)  | 4 (0.5 %)                                     | --      | 0 (0.0)   | 4 (0.5 %)                                     | --      |
| Death (any cause)                           | 4 (0.3 %)  | 4 (0.3 %)                                     | --      | 2 (0.2 %)  | 6 (0.7 %)                                     | --      | 0 (0.0)   | 2 (0.2 %)                                     | --      |
| VTE-related death                           | 0 (0 %)  | 1 (< 0.1 %)                                   | --      | 0 (0 %)  | 1 (0.1 %)                                     | --      | 0 (0)   | 0 (0 %)                                       | --      |

n = number of events; (%) = percentage

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.

## **INDICATIONS**

Xarelto is indicated for the prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks).

## **CONTRAINDICATIONS**

Xarelto is contraindicated in patients:

- hypersensitive to the active substance or to any of the excipients,
- with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding),
- with lesions at increased risk of clinically significant bleeding e.g. cerebral infarction (haemorrhagic or ischaemic) within the last 6 months and patients with spontaneous impairment of haemostasis,
- with hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see Pharmacokinetic properties),
- with severe renal impairment with a creatinine clearance < 15 mL/min (see Pharmacokinetic properties and PRECAUTIONS),
- concomitantly treated with strong inhibitors of both CYP3A4 and P-glycoprotein such as HIV protease inhibitors (e.g. ritonavir) or systemically administered azole anti-mycotics (e.g. ketoconazole) (see Interactions with Other Medicines).

Xarelto is contraindicated in pregnant women (see PRECAUTIONS, Use in Pregnancy). No human data are available for the use of rivaroxaban in pregnant women. Animal data show that rivaroxaban crosses the placental barrier.

Xarelto is contraindicated in breast-feeding women. No human data are available for use of rivaroxaban in nursing mothers. Animal data indicate that rivaroxaban is secreted into breast milk (see PRECAUTIONS, Use in Lactation).

## **PRECAUTIONS**

### **Haemorrhagic risk**

Due to the pharmacological mode of action, the use of Xarelto may be associated with a risk of occult or overt bleeding (see ADVERSE EFFECTS). 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. Any

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

#### *General haemorrhagic risk factors*

Xarelto like other antithrombotics should 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
- shortly after brain, spinal or ophthalmological surgery
- concomitant use of medicines affecting haemostasis

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

#### *Renal impairment*

Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (see Interactions with Other Medicines). 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. Due to the underlying disease these patients are also at an increased risk of both bleeding and thrombosis. Due to limited clinical data Xarelto should be used with caution in patients with CrCl 15 - 29 mL/min (see sections DOSAGE AND ADMINISTRATION, PHARMACOLOGY).

No clinical data are available for patients with severe renal impairment (CrCl < 15 mL/min). Therefore use of Xarelto is contraindicated in these patients (see CONTRAINDICATIONS).

#### *Hepatic impairment*

Xarelto is contraindicated in patients with hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. Xarelto may be used in cirrhotic patients with moderate hepatic (Child Pugh B) impairment if it is not associated with coagulopathy. (see PHARMACOLOGY and CONTRAINDICATIONS).

### *Strong CYP3A4 and P-gp inhibitors*

Xarelto is contraindicated in patients receiving concomitant systemic treatment withazole-antimycotics (e.g. ketoconazole) 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 CONTRAINDICATIONS and Interactions with Other Medicines). However, fluconazole is a less potent CYP3A4 and P-gp inhibitor and may be co-administered with caution.

### *Non-steroidal anti-inflammatory drugs*

Care should be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs) as these drugs may impact haemostasis (see Interaction with Other Medicines).

### *Anticoagulants*

Co-administration of Xarelto with other anticoagulants has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk. (see Interaction with Other Medicines)

### *Platelet aggregation inhibitors*

Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (e.g. clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk (see Interaction with Other Medicines). For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

## **Spinal/epidural anaesthesia or puncture**

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is performed, 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 should 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 Xarelto. The next Xarelto dose is to be administered not earlier than 6 hours after the removal of the catheter.

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

### **Lactose intolerance**

Xarelto contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Xarelto.

### **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, Xarelto is not recommended in these patients.

### **Effects on Fertility**

Rivaroxaban did not affect male or female fertility at oral doses up to 200 mg/kg/day in Wistar rats, which corresponds to 33-fold (males) and 49-fold (females) the unbound rivaroxaban AUC in humans at the maximum recommended dose.

### **Use in Pregnancy**

Pregnancy Category C

There are no data from the use of rivaroxaban in pregnant women. Thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss.

Studies in rats and rabbits were affected by the anticoagulant effects of rivaroxaban on the mother. In rats, altered placental appearance and necrosis were observed at doses  $\geq$  10 mg/kg/day (4 times human exposure based on unbound plasma AUC). A NOAEL in rats for embryofetal development was established at 35 mg/kg/day (17 times human exposure based on unbound plasma AUC).

In rabbits, abortions occurred at doses  $\geq$  10 mg/kg/day (11 times human exposure based on unbound plasma AUC), while deaths occurred at doses  $\geq$  40 mg/kg/day (52 times human exposure based on unbound plasma AUC). Changes in placental appearance (course, grained and/or necrotic) were also noted at doses  $\geq$  10 mg/kg/day. A NOAEL in rabbits for embryofetal development was established at 2.5 mg/kg/day (3 times human exposure based on unbound plasma AUC).

Animal data show that rivaroxaban crosses the placental barrier. Therefore Xarelto is contraindicated in pregnancy (see CONTRAINDICATIONS). Xarelto should be used in women of childbearing potential only with effective contraception.

### **Use in Lactation**

No data on the use of rivaroxaban in nursing mothers are available. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see CONTRAINDICATIONS).

[<sup>14</sup>C] rivaroxaban was administered orally to lactating Wistar rats (day 8 to 10 post partum) as a single oral dose of 3 mg/kg body weight. [<sup>14</sup>C] rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent in relation to the administered dose. The estimated amount of radioactivity excreted into milk was 2.12 % of the maternal dose within 32 hours after administration.

## **Paediatric Use**

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 (see DOSAGE AND ADMINISTRATION and Pharmacokinetic properties).

## **Use in Elderly**

No dose adjustment is required for the elderly (> 65 years of age). It should be taken into consideration that increasing age may be associated with declining renal and hepatic function. (see CONTRAINDICATIONS, PRECAUTIONS and Pharmacokinetic properties).

## **Different Gender and Different Weight Categories**

No dose adjustment is required for these patient populations (see "Pharmacokinetic properties").

## **Carcinogenicity**

Results from carcinogenicity studies are not yet available.

## **Genotoxicity**

Rivaroxaban showed no genotoxicity potential in bacterial mutagenicity tests, chromosomal aberration assays in Chinese hamster cells or in an *in vivo* mouse micronucleus assay.

## **Interactions with Other Medicines**

### ***Pharmacokinetic interactions***

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP3A4, CYP2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp)/breast cancer resistance protein (Bcrp) transporter systems.

### *CYP Inhibition*

Rivaroxaban does not inhibit CYP3A4 or any other major CYP isoforms.

### *CYP Induction*

Rivaroxaban does not induce CYP3A4 or any other major CYP isoforms.

### *Effects on rivaroxaban*

- *Strong inhibitors of both CYP3A4 and P-gp*

The concomitant use of Xarelto with substances that strongly inhibit both CYP3A4 and P-gp may lead to reduced hepatic and renal clearance and thus significantly increased systemic exposure of rivaroxaban.

Co-administration of Xarelto with the azole-antimycotic ketoconazole (400 mg o.d.), a strong CYP3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady

state AUC and a 1.7-fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in its pharmacodynamic effects.

Co-administration of Xarelto with the HIV protease inhibitor ritonavir (600 mg b.i.d.), a strong CYP3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean rivaroxaban  $C_{max}$ , with significant increases in its pharmacodynamic effects.

Therefore Xarelto is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see CONTRAINDICATIONS). However, fluconazole is a less potent CYP3A4 and P-gp inhibitor and may be co-administered with caution (see PRECAUTIONS and Table 3 below)

- *Strong inhibitors of CYP3A4 or P-gp*

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, increase rivaroxaban plasma concentrations to a level which is considered not clinically relevant. (see Table 3 below)

- *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. (see Table 3 below)

**Table 3:** Established or potential interactions

| <i>Class (effect)</i><br>Examples   | Effect on rivaroxaban plasma concentration | Clinical comment   |
|---|--|--|
| <i>Strong CYP3A4 and strong P-gp inhibitor</i><br>Azole-antimycotics<br>e.g. ketoconazole, itraconazole, voriconazole, posaconazole<br>or HIV-protease inhibitors<br>e.g. ritonavir | ↑ rivaroxaban                              | Concomitant treatment with systemic azole-antimycotics or HIV-protease inhibitors is contraindicated. However, fluconazole may be co-administered with caution.  |
| <i>Strong CYP3A4 and moderate P-gp inhibitor</i><br>Clarithromycin  | ↑ rivaroxaban                              | 500 mg b.i.d. led to a 1.5-fold increase in mean rivaroxaban AUC and a 1.4-fold increase in $C_{max}$ . This increase, which is close to the magnitude of the normal variability of AUC and $C_{max}$ , is considered to be not clinically relevant. |
| <i>Moderate CYP3A4 and moderate P-gp inhibitor</i>  | ↑ rivaroxaban                              | 500 mg t.i.d. led to a 1.3-fold increase in mean rivaroxaban steady state AUC and  |

|   |               |   |
|---|---------------|---|
| Erythromycin  |               | C <sub>max</sub> . This increase is within the magnitude of the normal variability of AUC and C <sub>max</sub> and is considered not clinically relevant.   |
| <i>Other P-gp inhibitors</i><br>Cyclosporine, Amiodarone,<br>Quinidine, Diltiazem,<br>Verapamil                             | ↑ rivaroxaban | Theoretically, due to the inhibition of P-gp mediated renal excretion, concomitant administration with Xarelto may lead to increased plasma rivaroxaban to a level which is considered not clinically relevant. |
| <i>Strong CYP3A4 and P-gp inducer</i><br>Rifampicin   | ↓ rivaroxaban | Led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The decrease in rivaroxaban plasma concentration is considered not clinically relevant.    |
| <i>Other CYP3A4 inducers</i><br>Anticonvulsants e.g.<br>Phenytoin,<br>Carbamazepine,<br>Phenobarbitone or<br>St John's wort | ↓ rivaroxaban | Concomitant use with Xarelto may lead to a decreased plasma rivaroxaban concentration.  |

### ***Pharmacodynamic interactions***

#### ***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. Co-administration of Xarelto with other anticoagulant therapy has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see PRECAUTIONS).

#### ***Non-steroidal anti-inflammatory drugs***

Bleeding time was prolonged after co-administration of naproxen (500 mg) and rivaroxaban (mean 11.3 minutes) as compared to naproxen (500 mg) alone (7.9 minutes) and rivaroxaban alone (6.1 minutes, normal range of bleeding time: 2 to 8 minutes). In the three Phase III trials (RECORD 1, 2, and 3) more than 70 % of subjects received concomitant NSAIDs with a similar risk of bleeding as compared to comparator treatment. However, due to the general impact on haemostasis, care should be taken if anticoagulated patients are treated concomitantly with NSAIDs (see PRECAUTIONS).

### *Platelet aggregation inhibitors*

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction. Bleeding time was prolonged after co-administration of clopidogrel and rivaroxaban (mean 21.7 minutes) as compared to clopidogrel alone (12.7 minutes) and rivaroxaban alone (7.7 minutes, normal range of bleeding time: 2 to 8 minutes) This increase in the combined treatment group was driven by a subset of patients in whom pronounced prolongations of bleeding times were observed. These prolongations of bleeding time did not correlate to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases. (see PRECAUTIONS).

### *Food and dairy products*

Xarelto can be taken with or without food (see Pharmacokinetic properties).

### *Interactions shown not to exist*

There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP3A4 and P-gp).

Co-administration of the H<sub>2</sub> receptor antagonist ranitidine, the antacid aluminium hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics.

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

## **Effect on Laboratory Tests**

Clotting parameter tests (PT, aPTT, HepTest<sup>®</sup>) are affected as expected by the mode of action of rivaroxaban. Xarelto at recommended doses, prolongs several global (prothrombin time, activated partial thromboplastin time, HepTest<sup>®</sup>) and specific (inhibition of factor Xa activity) clotting tests. Prothrombin time (PT) is influenced by Xarelto in a dose-dependent manner if Neoplastin<sup>®</sup> is used for the assay. In patients undergoing elective total hip replacement or knee replacement surgery, the 5/95 percentiles of PT (Neoplastin<sup>®</sup>) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 seconds. In case of excessive doses, the PT is expected to be outside of this range.

Although activated thromboplastin time (aPTT), antifactor Xa activity and HepTest<sup>®</sup> are also prolonged dose-dependently, neither test is recommended for assessment of the pharmacodynamic effects of Xarelto.

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

No effect of rivaroxaban on ability to drive or operate machinery has been reported.

## ADVERSE EFFECTS

The safety of Xarelto has been evaluated in four Phase III studies including 6097 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. In the population of subjects who have taken at least one dose of Xarelto 10 mg o.d., a total of 2717 subjects were included in the knee replacement trial with a scheduled treatment period of about 2 weeks and 3380 subjects included in the total hip replacement trials with a scheduled treatment period of about 5 weeks. The two treatment groups, rivaroxaban and enoxaparin/placebo showed very similar demographic and baseline characteristics.

The incidence of common treatment-emergent adverse reactions reported in the safety population was similar in both treatment groups for the four Phase III studies irrespective of treatment duration and for treatment period until Day 12 ± 2. The most frequently reported treatment-emergent adverse reactions in both treatment groups during both treatment periods were gastrointestinal disorders, in particular nausea; procedural complications such as post-operative anaemia; and investigations, in particular related to liver function tests.

Xarelto has not been studied for longer than 3 months in any completed trial.

The adverse events and adverse reactions are presented within each system organ class; and should be interpreted within the surgical setting.

Frequencies are defined as

|            |          |            |                           |
|------------|----------|------------|---------------------------|
| Common:    | ≥ 1 %    | to < 10 %  | (≥ 1/100 to < 1/10)       |
| Uncommon:  | ≥ 0.1 %  | to < 1 %   | (≥ 1/1,000 to < 1/100)    |
| Rare:      | ≥ 0.01 % | to < 0.1 % | (≥ 1/10,000 to < 1/1,000) |
| Very rare: | < 0.01 % |            | (< 1/10,000)              |

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 and organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including possible 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. patients with uncontrolled severe arterial hypertension and/or taking concomitant medications affecting haemostasis (see PRECAUTIONS). 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. Therefore, the possibility of a haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Adverse events and adverse reactions as reported by the investigators in the four Phase III studies are listed in Table 4 below by system organ class (in MedDRA).

RECORD 1-3 trials were similar in trial design and patient population, the dose regimen tested was rivaroxaban 10 mg o.d. compared to enoxaparin 40 mg o.d.

RECORD 4 provides additional safety information for rivaroxaban in the same dosage and patient population as RECORD 1-3. However in RECORD 4, the enoxaparin treatment group was given 30 mg b.i.d. This dosage regimen is not approved for use in New Zealand. Therefore safety data from RECORD 4 patients for enoxaparin have not been included in the table below.

Adverse events and adverse reactions as reported by the investigators in the four Phase III studies are listed in Table 4 below by system organ class (in MedDRA).

**Table 4:** Treatment-emergent adverse events (AE)  $\geq$  1 % (regardless of causality) and treatment emergent adverse reactions (ADR) starting after initiation of rivaroxaban, as reported by the investigators in patients in four Phase III studies 11354, 11357, 11356 and 11355

|  | <b>XARELTO<br/>(10 mg o.d.)<br/>N= 6097</b> |             | <b>Enoxaparin/Placebo<br/>(40 mg o.d.)<br/>N= 4692*</b> |             |
|--|---|-------------|---|-------------|
| <b>System Organ Class</b><br>Medical Entity/<br>Preferred Term | <b>AE</b>                                   | <b>ADR</b>  | <b>AE</b>   | <b>ADR</b>  |
| <b>Blood and lymphatic system disorders</b>                    |   |             |   |             |
| Anaemia (incl. respective lab parameters)                      | 361 (5.93%)                                 |             | 332 (7.08%)   | 55 (1.17 %) |
| <b>Cardiac disorders</b>                                       |   |             |   |             |
| Hypertension   | 92 (1.51%)                                  |             | 86 (1.83 %)   |             |
| Hypotension  | 246 (4.04%)                                 |             | 238 (5.07 %)  |             |
| Tachycardia  | 151 (2.48%)                                 |             | 71 (1.51 %)   |             |
| <b>Endocrine disorders</b>                                     |   |             |   |             |
| Hyperglycaemia   | 46 (0.76%)                                  |             | 53 (1.13 %)   |             |
| <b>Gastrointestinal disorders</b>                              |   |             |   |             |
| Nausea   | 673 (11.05%)                                | 106 (1.74%) | 519 (11.06 %)   | 86 (1.83 %) |
| Constipation   | 547 (8.98%)                                 |             | 335 (7.14 %)  |             |
| Diarrhoea  | 154 (2.53%)                                 |             | 137 (2.92 %)  |             |
| Dyspepsia  | 83 (1.36%)                                  |             | 51 (1.09 %)   |             |
| GI and abdominal pain  | 131 (2.15%)                                 |             | 93 (1.98 %)   |             |
| Vomiting   | 523 (8.59%)                                 |             | 482 (10.27 %)   |             |

|   | <b>XARELTO<br/>(10 mg o.d.)<br/>N= 6097</b> |             | <b>Enoxaparin/Placebo<br/>(40 mg o.d.)<br/>N= 4692*</b> |              |
|---|---|-------------|---|--------------|
| <b>System Organ Class</b><br>Medical Entity/<br>Preferred Term                  | <b>AE</b>                                   | <b>ADR</b>  | <b>AE</b>   | <b>ADR</b>   |
| <b>General disorders and administration site conditions</b>                     |   |             |   |              |
| Fever   | 799 (13.12%)                                | 94 (1.54%)  | 444 (9.46 %)  |              |
| Headache  | 151 (2.48%)                                 |             | 108 (2.30 %)  |              |
| Peripheral Oedema   | 416 (6.83%)                                 | 101 (1.66%) | 162 (3.45%)   |              |
| Unspecific pain   | 538 (8.83%)                                 |             | 295 (6.29 %)  |              |
| <b>Infections and infestations</b>  |   |             |   |              |
| Urinary tract infection   | 112 (1.84%)                                 |             | 90 (1.92 %)   |              |
| <b>Injury, Poisoning and Procedural Complications</b>                           |   |             |   |              |
| Arthralgia  | 110 (1.81%)                                 |             | 81 (1.73 %)   |              |
| Post procedural haemorrhage (incl. postoperative anaemia and wound haemorrhage) | 422 (6.93%)                                 | 125 (2.05%) | 279 (5.95 %)  | 109 (2.32 %) |
| Wound healing complications   | 214 (3.51%)                                 |             | 161 (3.43%)   |              |
| <b>Investigations</b>   |   |             |   |              |
| Increase in blood alkaline phosphatase  | 38 (0.82 %)                                 |             | 57 (1.21 %)   |              |
| Increase in transaminases   | 157 (2.58%)                                 | 118 (1.94%) | 208 (4.43 %)  | 137 (2.92 %) |
| Increased gamma-glutamyltransferase   | 109 (1.79%)                                 | 77 (1.26%)  | 126 (2.69 %)  | 73 (1.56 %)  |
| Increased lactate dehydrogenase   | 68 (1.12%)                                  |             | 56 (1.19 %)   |              |
| <b>Musculoskeletal and connective tissue disorders</b>                          |   |             |   |              |
| Increased muscle tone and cramping  | 163 (2.68%)                                 |             | 39 (0.83 %)   |              |
| <b>Nervous system disorders</b>   |   |             |   |              |
| Dizziness   | 259 (4.25%)                                 |             | 144 (3.07 %)  |              |
| Sleep disorders   | 321 (5.27%)                                 |             | 196 (4.18 %)  |              |
| Syncope   | 60 (1.29 %)                                 |             | 33 (0.70 %)   |              |
| Confusion and disorientation  | 71 (1.17%)                                  |             |   |              |

|  | <b>XARELTO<br/>(10 mg o.d.)<br/>N= 6097</b> |            | <b>Enoxaparin/Placebo<br/>(40 mg o.d.)<br/>N= 4692*</b> |            |
|--|---|------------|---|------------|
| <b>System Organ Class</b><br>Medical Entity/<br>Preferred Term | <b>AE</b>                                   | <b>ADR</b> | <b>AE</b>   | <b>ADR</b> |
| <b>Renal and urinary disorders</b>                             |   |            |   |            |
| Urinary retention  | 84 (1.80 %)                                 |            | 84 (1.79 %)   |            |
| <b>Respiratory, thoracic and mediastinal disorders</b>         |   |            |   |            |
| Dyspnoea   | 94 (1.54%)                                  |            | 58 (1.24 %)   |            |
| <b>Skin and subcutaneous tissue disorders</b>                  |   |            |   |            |
| Pruritus   | 243 (3.99%)                                 |            | 87 (1.85 %)   |            |
| Rash   | 97 (1.59%)                                  |            | 57 (1.21 %)   |            |
| Unspecific blistering  | 104 (1.71%)                                 |            | 43 (0.92 %)   |            |
| Erythema   | 109 (1.79%)                                 |            |   |            |
| <b>Social circumstances</b>                                    |   |            |   |            |
| Anxiety reaction   | 86 (1.41%)                                  |            | 39 (0.83 %)   |            |
| <b>Vascular disorders</b>                                      |   |            |   |            |
| Haematoma  | 80 (1.31%)                                  |            | 72 (1.53 %)   |            |
| Thrombocythaemia   | 121 (1.99%)                                 |            | 87 (1.85 %)   |            |
| Deep vein thrombosis   | 198 (4.25 %)                                |            | 363 (7.74 %)  |            |

\* Treatment-emergent AE/ADR after first dose of enoxaparin administration as reported by the investigators in three Phase III studies 11354, 11357, 11356

### **Less Common Clinical Trial Adverse Drug Reactions < 1 % in the four Phase III studies 11354, 11357, 11356, 11355:**

**Blood and the Lymphatic System Disorders:** Anaemia (incl. respective laboratory parameters), thrombocythaemia (incl. platelet count increased)

**Cardiac Disorders:** Tachycardia

**Gastrointestinal Disorders:** Constipation, diarrhoea, abdominal and gastrointestinal pain (incl. upper abdominal pain, stomach discomfort), dyspepsia (incl. epigastric discomfort), dry mouth, vomiting

**General Disorders and Administration Site Conditions:** Localised oedema, decreased general strength and energy (incl. fatigue, asthenia), feeling unwell (incl. malaise)

**Hepatobiliary disorders:** Hepatic function abnormal

**Immune system disorders:** Dermatitis allergic

**Injury, Poisoning and Procedural Complications:** Wound secretion

**Investigations:** Increased lipase, increased amylase, blood bilirubin increased, increased LDH, increased alkaline phosphatase, bilirubin conjugated increased (with or without concomitant increase of ALT)

**Musculoskeletal, Connective Tissue and Bone Disorders:** Pain in extremity

**Nervous System Disorders:** Dizziness, headache, syncope (incl. loss of consciousness)

**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

**Vascular Disorders:** Hypotension (incl. blood pressure decrease, procedural hypotension), haematoma (incl. rare cases of muscle haemorrhage), gastrointestinal tract haemorrhage (incl. gingival bleeding, rectal haemorrhage, haematemesis), urogenital tract haemorrhage, nose bleed

In other clinical studies with rivaroxaban, single cases of adrenal haemorrhage and conjunctival haemorrhage, and fatal gastrointestinal ulcer haemorrhage have been reported; jaundice and hypersensitivity were rare; haemoptysis was uncommon. Intracranial bleeding (especially in patients with arterial hypertension and/or on concomitant antihaemostatic agents) have been reported.

In other clinical studies, vascular pseudoaneurysm formation following percutaneous intervention has been reported.

Moreover, in other clinical studies and postmarketing surveillance, known complications secondary to bleeding, such as compartment syndrome, have been reported. Acute renal failure/renal failure secondary to bleeding event sufficient to cause hypoperfusion have also been reported.

## **DOSAGE AND ADMINISTRATION**

The recommended dose of Xarelto for VTE prevention in major orthopaedic surgery of the lower limbs (elective total hip or knee replacement) is a 10 mg tablet taken once-daily.

The initial dose should be taken 6 - 10 hours after surgery provided that haemostasis has been established. Xarelto may be taken with or without food. If a dose is missed the patient should take Xarelto immediately and continue on the following day with the once-daily intake as before.

The duration of treatment depends on the type of major orthopaedic surgery.

- For patients undergoing hip replacement surgery, a treatment duration of 5 weeks is recommended.

- For patients undergoing knee replacement surgery, a treatment duration of 2 weeks is recommended.

Dose of 10 mg once-daily and duration specified for each type of surgery is not to be exceeded.

#### *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 Pharmacokinetic properties).

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 must be used with caution in these patients (see PRECAUTIONS and Pharmacokinetic properties). No clinical data are available for patients with severe renal impairment (CrCl < 15 mL/min). Therefore, use of Xarelto is contraindicated in patients with CrCl < 15 mL/min (see CONTRAINDICATIONS).

#### *Hepatic impairment*

Xarelto is contraindicated in patients with hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see CONTRAINDICATIONS). No dose adjustment is necessary in patients with other hepatic diseases (see Pharmacokinetic properties).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see CONTRAINDICATIONS and Pharmacokinetic properties).

#### *Patients above 65 years*

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

#### *Body weight*

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

#### *Gender*

No dose adjustment is required for these patient populations (see Pharmacokinetic properties).

#### *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.

### *Ethnic differences*

No dose adjustment is required based on ethnic differences (see Pharmacokinetic properties).

## **OVERDOSAGE**

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

A specific antidote antagonising the pharmacoeutical effect of rivaroxaban is not available.

Activated charcoal may reduce absorption of the drug if given within up to 8 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

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 a terminal half-life between 5 and 13 hours (see Pharmacokinetic properties).
- 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 one of the following procoagulants may be considered:

- activated prothrombin complex concentrate (APCC)
- prothrombin complex concentrate (PCC)
- recombinant factor VIIa.

However, there is currently no experience with the use of these products in individuals receiving Xarelto.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no scientific rationale for benefit or experience with systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving Xarelto. Due to the high plasma protein binding, rivaroxaban is not expected to be dialysable.

## **PRESENTATION AND STORAGE CONDITIONS**

One tablet contains 10 mg rivaroxaban. The tablets are film-coated round, biconvex, light red immediate-release tablets of 6 mm diameter marked with a Bayer cross on one

side and “10” and a triangle on the other side. The tablets are supplied in packs of 3, 10, 15, 30, 100 tablets. Not all pack sizes may be marketed.

The tablets are packed in thermoformed PP/Aluminium foil blisters or PVC/PVDC/Aluminium foil blisters.

Shelf life is 3 years when stored below 30 °C.

## **NAME AND ADDRESS OF THE SPONSOR**

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## **MEDICINE CLASSIFICATION**

PRESCRIPTION ONLY MEDICINE

## **DATE OF PREPARATION**

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