SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Xaroban Tablets 10 mg

2. Qualitative and quantitative composition

Each Film Coated tablet contains:

Rivaroxaban 10 mg

3. Pharmaceutical Dosage form:

Tablets

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.

Converting from Vitamin K Antagonists (VKA)

Special populations

Renal impairment.

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

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).

Hepatic impairment

Xaroban Tablets is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

Elderly population

No dose adjustment..

Body weight

No dose adjustment.

Gender

No dose adjustment.

Paediatric population

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

Method of administration

For oral use.

Xaroban can be taken with or without food.

For patients who are unable to swallow whole tablets, Xaroban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.

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

4.3. Contraindications

Active clinically significant bleeding.

Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

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

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

Pregnancy and breast feeding .

4.4. Special warnings and precautions for use

<u>Haemorrhagic risk</u>

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. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

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

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

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. Xaroban 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 .

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

Interaction with other medicinal products

The use of Xaroban 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 .

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

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is to be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension

• other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)

• vascular retinopathy

• bronchiectasis or history of pulmonary bleeding.

Hip fracture surgery

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

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

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

At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

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

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

If an invasive procedure or surgical intervention is required, rivaroxaban 10 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

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

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

Elderly population

Increasing age may increase haemorrhagic risk .

Information about excipients

Rivaroxaban 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 Xaroban 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 .

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. (For patients with renal impairment.

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. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in $C_{max}$when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment.

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.

<u>Anticoagulants</u>

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.

<u>NSAIDs/platelet aggregation inhibitors</u>

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 .

Warfarin

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

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

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

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum)*) may also lead to reduced rivaroxaban

plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies

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

No clinically relevant interaction with food was observed.

Laboratory parameters

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

4.6. Pregnancy and lactation:

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

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

Breast feeding

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

4.7. Undesirable effects

Xaroban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported. 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 eleven phase III studies including 32,625 patients exposed to rivaroxaban .

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

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
Prevention of venous thromboembolism in medically ill patients	3,997	10 mg	39 days
Treatment of DVT, PE and prevention of recurrence	4,556	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
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings (≥4 %) were epistaxis (5.9 %) and gastrointestinal tract haemorrhage (4.2 %).

In total about 67% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events. About 22% of the patients experienced adverse events considered related to treatment as assessed by investigators. In patients treated with 10 mg Xaroban undergoing hip or knee

replacement surgery and in hospitalised medically ill patients, bleeding events occurred in approximately 6.8% and 12.6% of patients, respectively, and anaemia occurred in approximately 5.9% and 2.1% of patients, respectively. In patients treated with either 15 mg twice daily Xarelto followed by 20 mg once daily for treatment of DVT or PE, or with 20 mg once daily for prevention of recurrent DVT and PE, bleeding events occurred in approximately 27.8% of patients and anaemia occurred in approximately 2.2% 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. In patients treated for prevention of atherothrombotic events after an acute coronary syndrome (ACS), bleeding of any type or severity was reported with an event rate of 22 per 100 patient years. Anaemia was reported with an event rate of 1.4 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:

very common (≥ 1/10)

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 : 2 All treatment-emergent adverse reactions reported in patients in phase III studies

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocythemia (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		

Nervous system disorders			
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
	Tachycardia		
Vascular disorders			
Hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders			
Epistaxis, haemoptysis			
Gastrointestinal disorders			
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic function	Jaundice	

	abnormal		
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		
Musculoskeletal and connective tissue disorders			
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]			Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood	Bilirubin conjugated increased (with or without concomitant	

	alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]	

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

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

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

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of Xaroban 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 anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, 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 . 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 Xaroban.

Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post-marketing observations

The following adverse reactions have been reported post-marketing in temporal association with the use of Xaroban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.

Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).

Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000)).

Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

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

5.0. Pharmacological Properties:

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised 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).

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

The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests.

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 , 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 3: 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
Sympto-matic 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.

In addition to the phase III RECORD program, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under real-

life setting. Symptomatic VTE occurred in 57 (0.6%) patients in the rivaroxaban group (n=8,778) and 88 (1.0%) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomised studies.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Xaroban 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 Xaroban in all subsets of the paediatric population in the prevention of thromboembolic.

4.9. Preclinical Safety Data:

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

5. Pharmaceutical particulars

5.1. List of excipients

Microcrystalline Cellulose PH 102

Lactose Monohydrate Mesh 60

Silica Colloidal Anhydrous

Sodium Laurilsulfate

Croscarmellose sodium

Magnesium Stearate

Opadry II White

Purified Water

5.2. Incompatibilities

None stated.

5.3. Shelf life

2 Years

5.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

5.5. Nature and contents of container

Xaroban Tablet 10mg for commercial use is available in Alu-Alu blister pack of 10 tablets. 1 blister is packed in printed carton with the product name and batch details along with the information of the manufacturer.

5.6. Special precautions for disposal and other handling

Not stated

6. Marketing Authorisation Holder:

The Searle Company Limited
1st Floor, N.I.C.L. Building, Abbasi Shaheed Road,
P. O. Box. 5696, Karachi – 75530,
Pakistan.

7. Marketing authorisation number(s):

076284

8. Date of first authorisation

21-04-2014