XAROBAN
(Rivaroxaban)

15mg & 20mg

Tablets

WARNING

(A) PREMATURE DISCONTINUATION OF RIVAROXABAN INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature discontinuation of XAROBAN increases the risk of thrombotic events: Premature discontinuation of any oral anticoagulant, including XAROBAN, increases the risk of thrombotic events. If anticoagulation with XAROBAN is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
B. Spinal/epidural hematoma:
Epidural or spinal hematomas have occurred in patients treated with XAROBAN who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
• use of indwelling epidural catheters
• concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
• a history of traumatic or repeated epidural or spinal punctures
• a history of spinal deformity or spinal surgery
• optimal timing between the administration of XAROBAN and neuraxial procedures is not known.
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis

COMPOSITION

Each film-coated Tablet contains:
Rivaroxaban ……15mg

Each film-coated Tablet contains:
Rivaroxaban ……20mg

THERAPEUTIC INDICATIONS

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

DOSAGE AND ADMINISTRATION

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE, as indicated in the table below.

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

For patients with moderate or severe renal impairment where the decision has been taken for 15 mg once daily from Day 22 onwards, other presentations only containing 15 mg film-coated tablets are available

The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban immediately to ensure intake of 30 mg Rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Rivaroxaban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Rivaroxaban
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban therapy should be initiated once the INR is ≤ 2.5.
When converting patients from VKAs to Rivaroxaban, INR values will be falsely elevated after the intake of Rivaroxaban. The INR is not valid to measure the anticoagulant activity of Rivaroxaban, and therefore should not be used.
Converting from Rivaroxaban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban can contribute to an elevated INR.
In patients converting from Rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban. Once Rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Converting from parenteral anticoagulants to Rivaroxaban
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from Rivaroxaban to parenteral anticoagulants
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban dose would be taken.

Special populations
Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15 mg twice daily for the first 3 weeks.
Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting
No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min)
Hepatic impairment
Rivaroxaban 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 Rivaroxaban in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban is not recommended for use in children below 18 years of age.

Method of administration

For oral use.
The tablets are to be taken with food

For patients who are unable to swallow whole tablets, Rivaroxaban tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban 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. After the administration of crushed Rivaroxaban15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

CONTRAINDICATIONS

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Hemorrhagic risk
As with other anticoagulants, patients taking Rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs.
In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of hemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.
Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anemia after initiation of treatment. Any unexplained fall in hemoglobin 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. Rivaroxaban 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
Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Interaction with other medicinal products
The use of Rivaroxaban 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 hemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Risk of Hemorrhage in Acutely Ill Medical Patients at High Risk of Bleeding
Acutely ill medical patients with the following conditions are at increased risk of bleeding with the use of Rivaroxaban for primary VTE prophylaxis: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (i.e., undergoing acute, in-hospital cancer treatment), active gastroduodenal ulcer in the three months prior to treatment, history of bleeding in the three months prior to treatment, or dual antiplatelet therapy. Rivaroxaban is not for use for primary VTE prophylaxis in these hospitalized, acutely ill medical patients at high risk of bleeding.

Patients with prosthetic valves
On the basis of a study, use of Rivaroxaban is not recommended in patients who have had transcatheter aortic valve replacement (TAVR) because patients randomized to rivaroxaban experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen. The safety and efficacy of Rivaroxaban have not been studied in patients with other prosthetic heart valves or other valve procedures. Use of Rivaroxaban is not recommended in patients with prosthetic heart valves

Hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Rivaroxaban is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are hemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Rivaroxaban have not been established in these clinical situations.

Spinal/epidural anesthesia or puncture
When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma 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 hemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg or 20 mg rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia 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. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e., at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban. 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.

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome
Direct-acting oral anticoagulants (DOACs), including rivaroxaban, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Rivaroxaban 15 mg/ Rivaroxaban 20 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.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate hemostasis has been established as determined by the treating physician.

Elderly population
Increasing age may increase hemorrhagic risk.

Dermatological reactions
Serious skin reactions, including Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, have been reported during post-marketing surveillance in association with the use of rivaroxaban. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g., spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

DRUG INTERACTIONS

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 Rivaroxaban 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.
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 CR_{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 CR_{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.

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.

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk.

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.

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

FERTILITY, PREGNANCY AND LACTATION

Pregnancy
Safety and efficacy of Rivaroxaban 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, Rivaroxaban is contraindicated during pregnancy
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Rivaroxaban 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.

Adverse Drug Reactions

Summary of the safety profile
The safety of rivaroxaban has been evaluated in eleven phase III studies including 32,625 patients exposed to rivaroxaban (see Table 1).

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

Indication	**Number of patients***	**Maximum daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
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. 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 Rivaroxaban undergoing hip or knee replacement surgery and in hospitalized 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 Rivaroxaban 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 cardiovascular death and myocardial infarction 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 Rivaroxaban are summarized 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, hematoma			
Respiratory, thoracic and mediastinal disorders			
Epistaxis, hemoptysis			
Gastrointestinal disorders			
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic function abnormal	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalized 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)	Localized oedema[A]	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDH[A], increased lipase[A], increased amylase[A], increased GGT[A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound		Vascular pseudoaneurysm[C]	

haemorrhage), contusion, wound secretion[A]			

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 Rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post hemorrhagic 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. 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 hemoglobin/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 hemostasis. Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnea and unexplained shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischemia 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 Rivaroxaban. 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 Rivaroxaban. 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)).
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis (In the pooled phase III trials, these events were estimated as very rare (<1/10,000)).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

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 antagonizing 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. Management should be individualized 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 hemostasis with bleeding control procedures, fluid replacement and hemodynamic 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 Via (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 Via 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.
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 hemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

PHARMACOLOGICAL PROPERTIES

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 Normalized Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.
In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
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.
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests

Pharmacokinetic properties

Absorption
Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.
Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food.
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Rivaroxaban 10 mg, 15 mg

and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.
Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.
Distribution
Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litres.
Biotransformation and elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the fecal 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 metabolized via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.
Special populations
Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.
Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.
Different weight categories
Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.
Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.
Hepatic impairment
Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C.
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. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.
Pharmacokinetic data in patients
In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.
Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max}model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.
Paediatric population
Safety and efficacy have not been established for children and adolescents up to 18 years.

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. hemorrhagic 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.

Summary of Clinical Studies

Clinical efficacy and safety

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

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96; P<0.001 for non-inferiority). Among all randomised patients analyzed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 - 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 4.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the Hazard Ratio (HR) with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 5).

Table 4: Efficacy results from phase III ROCKET AF

Study population	**ITT analyses of efficacy in patients with non-valvular atrial fibrillation**		
Treatment dose	**Rivaroxaban 20 mg once daily** **(15 mg once daily in patients with moderate renal impairment)** **Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)** **Event rate (100 pt-yr)**	**HR (95% CI)** **p-value, test for superiority**
Stroke and non-CNS systemic embolism	269 (2.12)	306 (2.42)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51)	609 (4.81)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and myocardial infarction	659 (5.24)	709 (5.65)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99)	281 (2.22)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16)	27 (0.21)	0.74 (0.42 - 1.32) 0.308
Myocardial infarction	130 (1.02)	142 (1.11)	0.91 (0.72 - 1.16) 0.464

Table 5: Safety results from phase III ROCKET AF

Study population	**Patients with non-valvular atrial fibrillation[a)]**		
Treatment dose	**Rivaroxaban 20 mg once daily** **(15 mg once daily in patients with moderate renal impairment)** **Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)** **Event rate (100 pt-yr)**	**HR (95% CI)** **p-value**
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47 - 0.93) 0.019
Hemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96 - 1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073
a) Safety population, on treatment * Nominally significant			

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean $CHADS_2$ and HAS-BLED scores were both 2.0 in XANTUS, compared to a mean $CHADS_2$ and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.

These observations in clinical practice are consistent with the established safety profile in this indication.

Patients undergoing cardioversion

A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischemic attack, non-CNS systemic embolism, myocardial infarction (MI) and cardiovascular death) occurred in 5 (0.5%)

patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

A randomized, open-label, multicenter study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.

Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e., clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.

The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001, and HR 0.63; 95% CI 0.50-0.80; p<0.001, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.

The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomized controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (≥ 2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

Einstein DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all-cause mortality.

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomization date (median: 351 days). Rivaroxaban 20 mg once daily and Rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.

The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

In the Einstein DVT study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p < 0.0001 (test for non-inferiority); HR: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 ((95% CI: 0.47 - 0.95), nominal p value p=0.027) in favor of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

Table 6: Efficacy and safety results from phase III Einstein DVT

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dose and duration	**Rivaroxaban [a)]** **3, 6 or 12 months** **N=1,731**	**Enoxaparin/VKA[b)]** **3, 6 or 12 months** **N=1,718**
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)

Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

***** p < 0.0001 (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 7) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); HR: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) were slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a HR 0.493 (95% CI: 0.308 - 0.789).

Table 7: Efficacy and safety results from phase III Einstein PE

Study population	**4,832 patients with an acute symptomatic PE**	
Treatment dose and duration	**Rivaroxaban [a)]** **3, 6 or 12 months** **N=2,419**	**Enoxaparin/VKA[b)]** **3, 6 or 12 months** **N=2,413**
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)
Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

* p < 0.0026 (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749 - 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 8).

Table 8: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE

Study population	**8,281 patients with an acute symptomatic DVT or PE**	
Treatment dose and duration	**Rivaroxaban [a)]** **3, 6 or 12 months** **N=4,150**	**Enoxaparin/VKA[b)]** **3, 6 or 12 months** **N=4,131**
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 (<0.1%)	2 (<0.1%)
Fatal PE/death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily

b) Enoxaparin for at least 5 days, overlapped with and followed by VKA

***** p < 0.0001 (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 - 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a HR of 0.771 ((95% CI: 0.614 - 0.967), nominal p value p = 0.0244).

In the Einstein Extension study (see Table 9) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

Table 9: Efficacy and safety results from phase III Einstein Extension

Study population	**1,197 patients continued treatment and prevention of recurrent venous thromboembolism**	
Treatment dose and duration	**Rivaroxaban [a)]** **6 or 12 months** **N=602**	**Placebo** **6 or 12 months** **N=594**
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)
a) Rivaroxaban 20 mg once daily ***** p < 0.0001 (superiority), HR: 0.185 (0.087 - 0.393)		

In the Einstein Choice study (see Table 10) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

Table 10: Efficacy and safety results from phase III Einstein Choice

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**Rivaroxaban 20 mg once daily** **N=1,107**	**Rivaroxaban 10 mg once daily** **N=1,127**	**ASA 100 mg once daily** **N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0 (0.0%)	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)[+]	17 (1.5%)[++]	53 (4.7%)
* p<0.001(superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59) ** p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47) [+] Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal) [++] Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.32 (0.18-0.55), p<0.0001 (nominal)			

In addition to the phase III EINSTEIN programme, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy in clinical practice. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40 - 1.50), 0.91 (95% CI 0.54 - 1.54) and 0.51 (95% CI 0.24 - 1.07), respectively.

These results in clinical practice are consistent with the established safety profile in this indication.

Paediatric population

Treatment of VTE and prevention of VTE recurrence in pediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicenter pediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study.

The EINSTEIN Junior phase III study was a randomized, active-controlled, open-label multicenter clinical study in 500 pediatric patients (aged from birth to < 18 years) with confirmed acute VTE. There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 84/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomized 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children <2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 11 and 12 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalization of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165 patients in the comparator group. These findings were generally similar among age groups. There were 119 (36.2%) children with any treatment-emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

Table 11: Efficacy results at the end of the main treatment period

Event	**Rivaroxaban** **N=335***	**Comparator** **N=165***
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalization on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)
* FAS= full analysis set, all children who were randomized		

Table 12: Safety results at the end of the main treatment period

	Rivaroxaban	**Comparator**
	N=329*	**N=162***
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)
* SAF = safety analysis set, all children who were randomized and received at least 1 dose of study medicinal product		

The efficacy and safety profile of rivaroxaban was largely similar between the pediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the pediatric VTE population as compared to the DVT/PE adult population.

Patients with high-risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCL) < 50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischemic strokes and 3 myocardial infarctions). No events were reported in patients randomized to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Rivaroxaban in all subsets of the pediatric population in the prevention of thromboembolic events.

PRESENTATION

Xaroban (Rivaroxaban) 15 mg tablets are available in alu-alu blister pack of 10 Tablets.

Xaroban (Rivaroxaban) 20 mg tablets are available in alu-alu blister pack of 10 Tablets.

INSTRUCTIONS

- To be sold on the prescription of a registered medical practitioner only.

-Protect from sunlight, moisture and heat.

-Store below 30°C.

-Keep out of the reach of children.

REGISTRATION NUMBER

Xaroban 15mg Tablet: Reg. No. 088253

Xaroban 20mg Tablet: Reg. No. 088257 Mfg. Lic. No. 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan.

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