Summary of Product Characteristics for Pharmaceutical Products

1.Name of the medicinal product

Rivaroxaban Tablets 2.5 mg/10mg/15 mg/20mg

2.Qualitative and quantitative constitution

Each Film coated tablet contains

Rivaroxaban .. 2.5 mg/10 mg /15 mg/20 mg

Excipient(s) with known effect: Each film coated contains lactose monohydrate.

For a full list of excipients, see section 6.1.

3.Pharmaceutical form

Film-coated (immediate release) tablet.

Rivaroxaban 2.5 mg- Yellow,round biconvex film coated tablets,debossed with "R" on oneside and "2.5" on other side.
Rivaroxaban 10 mg - Pink, round, biconvex, film coated tablets, debossed with "R" on oneside and "10" on other side.
Rivaroxaban 15 mg – Brown, round, biconvex, film coated tablets, debossed with "R" onone side and "15" on other side.
Rivaroxaban 20 mg - Brown, triangle, biconvex, film coated tablets, debossed with "R" onone side and "20" on other side.

4.Clinical Particulars

4.1 Therapeutic indications

• Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks)
• Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillationand at least one additional risk factor for stroke
• Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for theprevention of recurrent DVT and PE
Rivaroxaban, in combination with aspirin, is indicated for the
• death) in patients with coronary artery disease (CAD) and/or peripheral arterydisease (PAD).

4.2 Dose and Method of Administration Dosage

VTE Prevention in total hip and knee replacement

The recommended dose of Rivaroxaban tablets for VTE prevention in major orthopaedic surgery of the lower limbs (elective total hip or knee replacement) is a 10 mg tablet taken oncedaily. The initial dose should be taken 6 - 10 hours after surgery provided that haemostasis hasbeen established. The duration of treatment depends on the type of major orthopaedic surgery.

• For patients undergoing hip replacement surgery, a treatment duration of 5 weeks is recommended.
• For patients undergoing knee replacement surgery, a treatment duration of 2 weeks is recommended. Dose of 10 mg once daily and duration specified for each type of surgery is not to be exceeded.

Stroke Prevention in Atrial Fibrillation

The recommended dose is 20 mg once daily. For patients with moderate renal impairment (Creatinine clearance: 30 – 49 mL/min), one 15 mg tablet of Rivaroxaban tablets should be taken once daily. Therapy with Rivaroxaban tablets should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding. **Cardioversion** Rivaroxaban can be initiated or continued in patients who may require cardioversion. For TOE-guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see Section 5.1).

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

The recommended dose for the initial treatment of acute DVT and PE is 15 mg Rivaroxaban tablets twice daily for the first three weeks followed by 20 mg Rivaroxaban tablets once daily for the continued treatment and the prevention of recurrent DVT and PE. During the initial 3 weeks of acute treatment 15 mg of Rivaroxaban tablets should be taken twice daily.
After the initial 3 weeks treatment Rivaroxaban tablets should be continued at 20 mg once daily. Therapy should be continued as long as the VTE risk persists. The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Following completion of six to twelve months therapy, based on an individual assessment of the risk of recurrent DVT or PE against the risk for bleeding, dose reduction to 10 mg Rivaroxaban tablets once daily may be considered.

Coronary artery disease (CAD) and/or peripheral artery disease (PAD).

The recommended dose for the prevention of major cardiovascular events in patients with CAD and/or PAD is one tablet of 2.5 mg Rivaroxaban tablets twice daily in combination with a daily dose of 100 mg aspirin. In patients with CAD and/or PAD, Rivaroxaban tablets 2.5 mg twice daily is not indicated in combination with dual antiplatelet therapy (see Section 5.1). Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

Method of administration

Rivaroxaban tablets 2.5 mg tablets and 10 mg tablets may be taken with or without food (see Section 5.2). Rivaroxaban tablets 15 mg tablets and Rivaroxaban tablets 20 mg tablets should be taken with food (see Section 5.2). For patients who are unable to swallow whole tablets; Rivaroxaban tablets 2.5 mg, 10 mg, 15 mg, or 20 mg tablets may be crushed and mixed with water or apple sauce immediately prior to use and administered orally. After the administration of crushed Rivaroxaban tablets 15 mg or 20 mg tablets, the dose should be immediately followed by food. The crushed Rivaroxaban tablets 2.5 mg, 10 mg, 15 mg, or 20 mg tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering Rivaroxaban tablets. 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 theadministration of crushed Rivaroxaban tablets 15 mg or 20 mg tablets, the dose should beimmediately followed by enteral feeding (see Section 5.2). An in vitro compatibility study indicated that there is no adsorption of rivaroxaban from a water suspension of a crushed Rivaroxaban tablets tablet to PVC or silicone nasogastric (NG) tubing.

Special Populations

Elderly (Patients above 65 years)

Based on clinical data, no dose adjustment is required for these patient populations (see Section 5.2). Increasing age is associated with declining renal function. The risk of bleeding increases with increasing age (see Section 4.4).

Renal impairment

Prior to commencing treatment with Rivaroxaban tablets, an accurate assessment of renal function should be undertaken, especially if there is any suspicion that the personmay have a degree of renal impairment (see Section 5.2). No clinical data are available for patients with (CrCl < 15 mL/min) or patients on dialysis. Therefore, use of Rivaroxaban tablets is contraindicated in this patient population
(see Section 4.3).

Table 1 below for dosing instructions for patients with renal impairment by indications.

Table 1: Dosage and administration advice for patients with reduced renal function

<table>
<tr><th>Indication
Creatinine Clearance (CrCl)</th><th>VTE Prevention intotal hip and knee replacement</th><th>Stroke Prevention in Atrial Fibrillation</th><th>Treatment of DVT and PE and prevention of recurrent DVT and PE</th><th>Treatment of CAD and/or PAD</th></tr>
<tr><td>Normal
> 80 mL/min</td><td rowspan="3">10 mg once daily (Use with caution)</td><td>20 mg once daily</td><td>15 mg twice daily for 3 weeks, followed by</td><td>2.5 mg Rivaroxaban</td></tr>
<tr><td>Mild
50 – 80 mL/min</td><td>15 mg once daily</td><td>20 mg once daily for 6 to 12 months, then</td><td>tablets twice daily with 100 mg</td></tr>
<tr><td>Moderate
30 – 49 mL/min</td><td></td><td>maintain 20 mg once daily or consider* 10 mg once daily</td><td>aspirin once daily. Mild</td></tr>
<tr><td>Severe
15 – 29 mL/min</td><td rowspan="3">Rivaroxaban tablets is contraindicated</td><td rowspan="3">2.5 mg Rivaroxaban tablets twice daily with 100 mg aspirin once daily (Use with caution).</td></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
</table>

Severe **< 15 mL/min**	Rivaroxaban tablets is contraindicated

* Based on an individual assessment of the risk of recurrent DVT or PE against the risk forbleeding, dose reduction to 10 mg Rivaroxaban tablets once daily may be considered.

Hepatic impairment

Rivaroxaban tablets is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see Section 4.3 and Section No dose adjustment is necessary in patients with other hepatic diseases (see Section 5.2).
Limited clinical data in patients with moderate hepatic impairment (Child-Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child-Pugh C) (see Section 4.3 and Section 5.2)

Paediatric population)

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

Body Weight

No dose adjustment is required for these patient populations (see Section 5.2).

Gender

No dose adjustment is required for theses patient populations (see Section 5.2).

Ethnic differences

No dose adjustment is required based on ethnic differences (see Section 5.2).

Transition Rivaroxaban tablets from and to vitamin K antagonists (VKA) or parenteralanticoagulants

Anticoagulant	**Transition From Rivaroxaban tablets**	**Transition To Rivaroxaban tablets**
Vitamin K Antagonists	**Transition from Rivaroxaban tablets to VKAs:**	**Transition from VKA to Rivaroxaban tablets:**
Anticoagulant	**Transition From Rivaroxaban tablets**	**Transition To Rivaroxaban tablets**
(VKA)	**There is a potential for inadequate anticoagulation during the transition from Rivaroxaban tablets to VKA. Limited clinical trial data is available to guide the process whereby patients are converted from Rivaroxaban tablets to VKAs. Continuous adequate anticoagulation should be ensured during transition to an alternate anticoagulant.** **In patients converting from Rivaroxaban tablets to VKA, VKA should be given concurrently until the INR is ≥ 2.0. It**	**For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban tablets therapy should be initiated once the INR is ≤ 3.0.** **For patients treated for DVT and prevention of recurrent DVT and PE, VKA treatment should be stopped and Rivaroxaban tablets therapy**

Parenteral Anticoagulants	**should be noted that Rivaroxaban tablets can contribute to an elevated INR and so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of VKA. Therefore, INR measurements should be made in accordance with the following guidance during the transition from Rivaroxaban tablets to VKA:** **For the first two days of the conversion period, standard initial dosing of VKA should be used and, after the first two days, VKA dosing should be guided by INR testing. While patients are on both Rivaroxaban tablets and VKA, INR should be tested just prior to the next dose of Rivaroxaban tablets (not earlier than 24 hours after the previous dose). Once Rivaroxaban tablets is discontinued INR testing may be done reliably at least 24 hours after the last dose Transition from Rivaroxaban tablets to** **Parenteral Anticoagulants:**	**should be initiated once the INR is ≤ 2.5.** **The INR is not a valid measure for the anticoagulant activity of Rivaroxaban tablets, and therefore should not be used. The INR is only calibrated and validated for VKAs and cannot be used for any other anticoagulant.** **When switching patients from VKAs to Rivaroxaban tablets, INR values will be elevated after the intake of Rivaroxaban tablets but this is not indicative of the anticoagulant effect of Rivaroxaban tablets (see Section 4.5).** **Transition from Parenteral Anticoagulants to Rivaroxaban**
Anticoagulant	**Transition From Rivaroxaban tablets**	**Transition To Rivaroxaban tablets**
	Discontinue Rivaroxaban tablets and give the first **dose of parenteral anticoagulant at the** **time that the next Rivaroxaban tablets dose would** **be taken**	**tablets:** **For patients currently receiving a parenteral anticoagulant, start Rivaroxaban tablets zero to Two hours before the time of the next scheduled administration of the parenteral drug (e.g., LMWH) or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous** **unfractionated heparin).**

Missed dose

It is essential to adhere to the dosage schedule provided.

•Rivaroxaban tablets 2.5 mg tablets taken twice a day:

If a dose is missed the patient should continue with the regular dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

• Rivaroxaban tablets 10 mg, 15 mg or 20 mg tablets taken once a day:

If a dose is missed, the patient should take Rivaroxaban tablets immediately on the same day and continue on the following day with the once daily intake as before. A double dose should not be taken to make up for a missed tablet.

• Rivaroxaban tablets 15 mg tablets taken twice a day:

If a dose is missed during the 15 mg twice daily treatment phase the patient should take the next dose immediately to ensure the intake of 30 mg total dose per day. In this case two 15 mg tablets may be taken at once. The following day the patient should continue with the regular 15 mg twice daily intake schedule as recommended.

4.3 CONTRAINDICATIONS

Rivaroxaban tablets is contraindicated in patients:

• with clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding)

• with lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis

• with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk (see Section 4.4).

• undergoing dialysis or patients with severe renal impairment with a creatinine clearance < 30 mL/min for Rivaroxaban tablets 15 mg and 20 mg tablets, (CrCl < 15 mL/min for Rivaroxaban tablets 2.5 mg and 10 mg) due to increased plasma levels which may lead to an increased risk of bleeding (see Section 4.4)

• concomitantly treated with strong inhibitors of both CYP 3A4 and P-glycoprotein such as HIV protease inhibitors (e.g. ritonavir) or systemically administered azole anti-mycotics (e.g. ketoconazole) (see Section 4.5).

• who are pregnant or breast-feeding (see Section 4.6).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

Rivaroxaban tablets is contraindicated in patients with significant hepatic disease (including moderate to severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. Limited clinical data in patients with moderate hepatic impairment (Child-Pugh B) indicate a significant increase in the pharmacological activity. Rivaroxaban tablets may be used in cirrhotic patients with moderate hepatic (Child-Pugh B) impairment if it is not associated with coagulopathy (see Section 5).

Use in renal impairment

Rivaroxaban tablets is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 – 49 mL/min) receiving co-medications (including moderate inhibitors of CYP3A4 or P-gp) leading to increased

rivaroxaban plasma concentrations (see the underlying disease these patients are also at an increased risk of both bleeding and thrombosis. Due to limited clinical data Rivaroxaban tablets 2.5 mg and 10 mg
should be used with caution in patients with CrCl 15 – 29 mL/min. Rivaroxaban tablets 15 mg and 20 mg should not be used in patients with CrCl < 30 mL/min. Patients on dialysis have notbeen studied. Rivaroxaban tablets should not be used in this population (see Section 4.3). No clinical data are available for patients with creatinine clearance less than 15 mL/min. Therefore, use of Rivaroxaban tablets is contraindicated in these patients (see Section 4.3).

Use in the elderly
No dose adjustment is required for the elderly (> 65 years of age). It should be taken into consideration that increasing age may be associated with declining renal and hepatic function (see Section 4.3).
For prevention of major cardiovascular events in patients with CAD and /or PAD ≥ 75 years ofage in combination with aspirin 100 mg once daily:
- Caution should be used in these patients due to their higher bleeding risk. The benefit-risk ofthe treatment should be individually assessed on a regular basis. (see Section 5.1).

Paediatric use

Rivaroxaban tablets is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy (see Section 4.2 and Section 5.2).

Effects on laboratory tests

Rivaroxaban tablets at recommended doses prolongs the global clotting tests prothrombin time(PT), activated partial thromboplastin time (aPTT), HepTest, as well as the specific clotting test, anti-Factor Xa activity. PT is influenced by Rivaroxaban tablets in a dosedependent manner if Neoplastin is used for the assay. The 5/95 percentiles of PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) is described in Table 9 (see Section 5.1). In case of excessive doses, the PT is expected to be outside of this range. Although aPTT, anti-Factor Xa activity and HepTest are also prolonged dose-dependently, none of these reliably assesses the pharmacodynamic effects of Rivaroxaban tablets.

During any of warfarin and onwards, all tests (including PT, aPTT, anti-Factor Xa activity and ETP) only reflected the effect of rivaroxaban (see Section 4.2). INR is not a valid measure for the anticoagulant activity of rivaroxaban, and therefore should not be used. If measurement of rivaroxaban exposure is required in special clinical situations (such as suspected overdose, or emergency settings), both prothrombin time and chromogenic anti-Factor Xa assays using validated rivaroxaban calibrators and controls have the potential toassess rivaroxaban plasma concentration gravimetricall (ng/mL or µg/L).The pharmacokinetic profile of rivaroxaban has to be taken into account when interpreting resultsof these tests.

Haemorrhagic risk

Like other anticoagulants, Rivaroxaban tablets increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe Rivaroxaban tabletsRivaroxaban tablets to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of

bleeding. Due to the pharmacological mode of action, the use of Rivaroxaban tablets may be associated with an increased risk of occult or overt bleeding which may result in posthaemorrhagic anaemia (see Section 4.8). Several sub-groups of patients as detailed below are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. Patients at high risk of bleeding should not be prescribed Rivaroxaban tablets (see Section 4.3).
Close clinical surveillance is recommended in presence of multiple risk factors for bleeding including pharmacokinetic factors (renal impairment, hepatic impairment, drug interactions), pharmacodynamic interactions (NSAIDs, platelet aggregation inhibitors) and general haemorrhagic risk factors (see below).
General haemorrhagic risk factors

Rivaroxaban tablets like other antithrombotics should be used with caution in patients with an increased bleeding risk such as:
• congenital or acquired bleeding disorders

• uncontrolled severe arterial hypertension

• active ulcerative gastrointestinal disease

• recent gastrointestinal ulcerations

• vascular retinopathy

• recent intracranial or intracerebral haemorrhage

• intraspinal or intracerebral vascular abnormalities

• shortly after brain, spinal or ophthalmological surgery

• bronchiectasis or history of pulmonary bleeding.

• Patients with haemorrhagic or lacunar stroke

CAD and/ or PAD patients with previous haemorrhagic or lacunar stroke were not studied. Treatment with Rivaroxaban tablets 2.5 mg twice daily in combination with aspirin 100 mg once daily should be avoided in these patients.
• Patients with ischemic, non-lacunar stroke

• Care should be taken if patients are treated concomitantly with drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, other antithrombotics, or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs), (see Section 4.5).
• For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see Section 4.5).

Different gender and different weight categories

No dose adjustment is required for these patient populations (see Section 5.2).

Strong CYP 3A4 and P-gp inhibitors

Rivaroxaban tablets is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. Ritonavir). These active substances are strong inhibitors of both

CYP 3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see Section 4.3). However, fluconazole, a less potent CYP3A4 and P-gp inhibitor has less effect on rivaroxaban and may be coadministered (Table 2 and Table 3). **Concomitant medications**

Non-steroidal anti-inflammatory drugs

Care should be taken if patients are treated concomitantly with non-steroidal antiinflammatorydrugs (NSAIDs) as these drugs may impact haemostasis (see Section 4.5).

Anticoagulants

Co-administration of Rivaroxaban tablets with other anticoagulants has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (seeSection 4.5).

Platelet aggregation inhibitors

Care should be taken if patients are treated concomitantly with platelet aggregation inhibitors (e.g. clopidogrel and acetylsalicylic acid) as it may lead to an increased bleeding risk (see Section 4.5). For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Management of bleeding

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

•Identify and treat the underlying cause of the bleeding.

• Where no source of bleeding can be identified, delay of next rivaroxaban administration ordiscontinuation of treatment as appropriate. Rivaroxaban has a terminal half-life between 5and 13 hours (see Section 5.2). Management should be individualised according to the severity and location of the haemorrhage. A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. Because of high plasma protein binding, rivaroxaban is notexpected to be dialysable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

• Appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If life threatening bleeding cannot be controlled by the above measures, administration of oneof the following procoagulants may be considered:

• activated prothrombin complex concentrate (APCC)

• prothrombin complex concentrate (PCC)

• recombinant factor VIIa

While there is currently no experience with the use of these products in individuals receiving Rivaroxaban tablets, all three procoagulants have demonstrated significant reductions in rivaroxaban-induced bleeding time prolongation in nonclinical studies.There is no experiencewith antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving Rivaroxaban tablets. There is neither scientific rationale for benefit nor experience with thesystemic haemostatics desmopressin and aprotinin in

individuals receiving Rivaroxaban tablets.

Surgery and interventions

If an invasive procedure or surgical intervention is required, based on clinical judgement of the physician, Rivaroxaban tablets 10 mg, 15 mg and 20 mg should be stopped at least 24 hours and Rivaroxaban tablets 2.5 mg at least 12 hours before the intervention if possible. Individual patient factors will need to be taken into account in the decision as to how long Rivaroxaban tablets should be stopped prior to surgery. Consider longer duration of treatment cessation based on benefit/risk with patients at higher risk of bleeding or in cases of major surgery where complete haemostasis may be required. A specific agent to reverse the anti-coagulant effect of rivaroxaban is not yet available. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.Rivaroxaban tabletsRivaroxaban tablets 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 (see Section 5.2 and Section 4.4).

Patients with prosthetic heart valves

Rivaroxaban tablets is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). In the GALILEO study, patients randomised to Rivaroxaban tablets experienced higher rates of all-cause mortality, thromboembolic and bleeding events compared to those randomised to an antiplatelet regimen. The safety and efficacy of Rivaroxaban tablets have not been studied in patients with other prosthetic heart vlves or other valve procedures; therefore, there are no data to support that Rivaroxaban tablets provides adequate anti-coagulation in those patient populations Treatment with Rivaroxaban tablets is not recommended for these patients.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome, particularly high-risk patients (patients who are triple positive for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2- glycoprotein I antibodies). Treatment with rivaroxaban is associated with an increased rate of recurrent thrombotic events compared with vitamin K antagonists (VKA) in patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome and are persistently triple positive (see section 5.1)

Spinal / epidural anaesthesia or puncture

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

anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.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. The exact timing to reach a sufficiently low anti coagulant effect in each patient is not known. An young patients and 26 hours in elderly patients) after the last administration of

Rivaroxaban tablets (see Section 5.2).

The next Rivaroxaban tablets dose is to be administered not earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs the administration of Rivaroxaban tabletsis to be delayed for 24 hours.There is no clinical experience with the use of 2.5 mg twice daily with aspirin in these situations.There is no clinical experience with the use of 15 mg and 20mg rivaroxaban, therefore the use of indwelling epidural catheters is not recommended in these situations.

Hip fracture surgery

Rivaroxaban tablets has not been studied in interventional clinical trials in patients undergoinghip fracture surgery to evaluate efficacy and safety in these patients.

DVT and PE treatment: Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

Information about excipients

Lactose intolerance

Rivaroxaban contains lactose Patients with rare hereditary problems of lactose or galactose intolerance the Lapp lactase deficiency or glucose-galactose malabsorption should not takeRivaroxaban

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OFINTERACTIONS

Pharmacokinetic interactions

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepaticmetabolism and renal excretion of the unchanged drug, involving the Pglycoprotein (P-gp) / breast cancer resistance protein (Bcrp) transporter systems.

CYP Inhibition

Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.

CYP Induction

Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

Effects on rivaroxaban

• Strong inhibitors of both CYP3A4 and P-gp

The concomitant use of Rivaroxaban tablets with substances that strongly inhibit both CYP 3A4 and P-gp may lead to reduced hepatic and renal clearance and thus significantly increased systemic exposure of rivaroxaban.
Co-administration of Rivaroxaban tablets with the azole-antimycotic ketoconazole (400 mg od), a strong CYP 3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady state AUC and a 1.7-fold increase in mean rivaroxaban Cmax, with significant increases in its pharmacodynamic effects.Co-administration of Rivaroxaban tablets with the HIV protease inhibitor ritonavir (600 mg bid), a strong CYP 3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6-fold increase in mean rivaroxaban Cmax, with significant increases in its pharmacodynamic effects.Therefore, Rivaroxaban tabletsRivaroxaban tablets is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see Section 4.3). However, fluconazole (400 mg once daily) considered a less potent CYP3A4 and P-gp inhibitor led to an increase in rivaroxaban AUC and Cmax within the magnitude of normal variability (see Section 4.4 and Table 2, Table 3).

• Strong inhibitors of CYP3A4 or P-gp

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, increase rivaroxaban plasma concentrations to a level which is considered not clinically relevant (see Table 3).
Patients with renal impairment taking P-gp and weak to moderate CYP 3A4 inhibitors may have significant increases in exposure, which may increase bleeding risk. Rivaroxaban tablets is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) receiving co-medications (including moderate inhibitors of CYP3A4 or P-gp) leading to increased rivaroxaban plasma concentrations (see Section 4.4).

• CYP3A4 inducers

The concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. Rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma concentrations. Strong CYP 3A4 inducers must be used with caution in CAD and/or PAD patients treated with 2.5 mg Rivaroxaban tablets twice daily.
Caution should be taken when Rivaroxaban tabletsRivaroxaban tablets 15 and 20 mg tablets are coadministered with strong CYP3A4 inducers (see Table 3).

Table 2: Established or potential interactions which are clinically relevant

Class (effect) Examples	**Effect on rivaroxaban plasma concentration**	**Clinical comment**

Strong CYP3A4 and strong P-gpinhibitor Azole-antimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole or HIV-protease inhibitors e.g. ritonavir	↑ rivaroxaban	Concomitant treatment withsystemic azole antimycotics or HIV-proteaseinhibitors is contraindicated.

Table 3: Established or potential interactions which are not clinically relevant

Class (effect) Examples	Effect on rivaroxaban plasma concentration	Clinical comment
CYP3A4 and P-gp inhibitor Fluconazole	↑ rivaroxaban	Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.4-fold increase in mean rivaroxaban AUC and a 1.3-fold increase in mean Cmax. This increase is within the magnitude of the normal variability of AUC and Cmax and is considered not clinically relevant.
Strong CYP 3A4 and moderate P-gp inhibitor Clarithromycin	↑ rivaroxaban	500 mg bid led to a 1.5-fold increase in mean rivaroxaban AUC and a 1.4-fold increase in Cmax. This increase, which is close to the magnitude of the normal variability of AUC and Cmax, is considered to be not clinically relevant.
Moderate CYP3A4and moderate P-gp inhibitor Erythromycin	↑ rivaroxaban	500 mg tid led to a 1.3-fold increase in mean rivaroxaban steady state AUC and Cmax. This increase is within the magnitude of the normal variability of AUC and Cmax and is considered not clinically relevant.
Other P-gp inhibitors Cyclosporine, Amiodarone, Quinidine, Diltiazem, Verapamil	↑ rivaroxaban	Theoretically, due to the inhibition of P-gp mediated renal excretion, concomitant administration with Rivaroxaban tablets may lead toincreased plasma rivaroxaban to a level which is considered not clinically relevant.

Strong CYP 3A4 and P-gp inducer Rifampicin	↓ rivaroxaban	Led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The decrease in rivaroxaban plasma concentration is considered not clinically relevant.
Other CYP 3A4 Inducers Anticonvulsants e.g. Phenytoin, Carbamazepine, Phenobarbitone or St John's Wort	↓ rivaroxaban	Concomitant use with Rivaroxaban tablets may lead to a decreased plasma rivaroxaban concentration.

Pharmacodynamic interactions

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Co administration of Rivaroxaban Tablets with other anticoagulant therapy has not been studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk (see Section 4.4).

Converting patients from warfarin (INR 2.0 to 3.0) to Rivaroxaban Tablets 20 mg or from Rivaroxaban Tablets (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. It should be noted that the anticoagulant effect of rivaroxaban does not correlate to INR values and therefore INR should not be used. If it is desired to test the pharmacodynamic effects of Rivaroxaban Tablets during the conversion period, anti-Factor Xa activity, PiCT, and HepTest can be used as these tests were not affected by warfarin. From day 4 after stopping warfarin onwards, all tests (including PT, aPTT, inhibition of Factor Xa activity and ETP) reflected only the effect of Rivaroxaban Tablets (see Section 4.2).

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough 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 Tablets.

Non-steroidal anti-inflammatory drugs

Bleeding time was prolonged after co-administration of naproxen (500 mg) and rivaroxaban (mean 11.3 minutes) as compared to naproxen (500 mg) alone (7.9 minutes) and rivaroxaban alone (6.1 minutes, normal range of bleeding time: 2 to 8 minutes). In the three Phase III trials (RECORD 1, 2, and 3) more than 70% of subjects received concomitant NSAIDs with a similar risk of bleeding as compared to comparator treatment. However, due

to the general impact on haemostasis, care should be taken if anticoagulated patients are treated concomitantly with NSAIDs (see Section 4.4). No clinically relevant prolongation of bleeding time was observed after concomitant administration of Rivaroxaban Tablets (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with more pronounced pharmacodynamic response(see Section 4.4).

Platelet aggregation inhibitors

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction (with Rivaroxaban Tablets 15 mg). Bleeding time was prolonged after co-administration of clopidogrel and rivaroxaban (mean 21.7 minutes) as compared to clopidogrel alone (12.7 minutes) and rivaroxaban alone (7.7 minutes, normal range of bleedingtime: 2 to 8 minutes). This increase in the combined treatment group was driven by a subset ofpatients in whom pronounced prolongations of bleeding times were observed. These prolongations of bleeding time did not correlate to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases (see Section 4.4).

Selective Serotonin Reuptake Inhibitors or Selective Norepinephrine Reuptake Inhibitors

in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical program, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Food and dairy products

Rivaroxaban Tablets 2.5 mg and 10 mg tablets can be taken with or without food (see Section.5.2). Rivaroxaban Tablets 15 mg and 20 mg tablets should be taken with food (Section 5.2).

Interactions shown not to exist

There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam(substrate of CYP 3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP 3A4 and P-gp).Co-administration of the H2 receptor antagonist ranitidine, the antacid aluminium hydroxide / magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics. No clinically significant pharmacokinetic orpharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid (see Section 4.4)

FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy - Pregnancy Category C

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

Studies in rats and rabbits were affected by the anticoagulant effects of rivaroxaban on themother. In rats, altered placental appearance and necrosis

were observed at doses ≥ 10 mg/kg/day (4 times human exposure based on unbound plasma AUC). A NOAEL in rats for embryofoetal development was established at 35 mg/kg/day (17 times human exposure based on unbound plasma AUC).

In rabbits, abortions occurred at doses ≥ 10 mg/kg/day (11 times human exposure based on exposure based on unbound plasma AUC). Changes in placental appearance (course, grained and/or necrotic) were also noted at doses ≥ 10 mg/kg/day. A NOAEL in rabbits for embryofoetal development was established at 2.5 mg/kg/day (3 times human exposure based on unbound plasma AUC). In rats and rabbits rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g., haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban tablets is contraindicated in pregnancy (see Section 4.3).
Rivaroxaban tablets should be used in women of childbearing potential only with effective contraception.

Use in lactation

No data on the use of rivaroxaban in nursing mothers are available. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, Rivaroxaban tabletsRivaroxaban tablets is contraindicated during breast-feeding (see Section 4.3). [^{14}C] rivaroxaban was administered orally to lactating Wistar rats (day 8 to 10 postpartum) as a single oral dose of 3 mg/kg body weight. [14C] rivaroxaban-related radioactivity was secreted into the milk of lactating rats only to a low extent in relation to the administered dose. The estimated amount of radioactivity excreted into milk was 2.12 % of the maternal dose within 32 hours after administration.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Syncope and dizziness have been reported and may affect the ability to drive and use machines (see Section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 UNDESIRABLE EFFECTS

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.
The safety of rivaroxaban has been evaluated in ten Phase III studies including 36,647 patients exposed to rivaroxaban (see Table 4).

Table 4: Number of patients studied and treatment duration in Phase III studies

Indication	Number of patients	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT, PE and prevention of recurrent DVT and PE	6,790	Day 1 – 21: 30 mg Day 22 and onwards: 20 mg After at least six months: 10 mg or 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 major cardiovascular events (composite of stroke, myocardial infarction and cardiovascular death) in patients with coronary artery disease (CAD) and/or peripheral artery disease (PAD).	18,244	2.5 mg bid combination with 100 mg od aspirin or 5 mg bid alone	47 months

In total about 69% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events (regardless of causality). About 24% of patients experienced adverse events considered related to treatment as assessed by investigators.

Table 5: Bleeding and anaemia events rates in patients exposed to Rivaroxaban across the completed phase III studies

Indication	Any Bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Treatment of DVT, PE and prevention of recurrent DVT, PE	23% of patients	1.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years

Due to the pharmacological mode of action, the use of Rivaroxiban may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in posthaemorrhagic anaemia. The signs, symptoms, and severity (including possible fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or taking concomitant medications affecting haemostasis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, asthenia, 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 Rivaroxiban. Therefore, the possibility of a haemorrhage is to be considered in evaluating the condition in any anticoagulated patient. Results from the COMPASS clinical trial showed bleeding incidence rates of 6.7 per 100 patient years and anaemia incidence rates of 0.15 per 100 patient years1.

1 A pre-specified selective approach to adverse event collection was applied.

VTE Prevention in total hip and knee replacement The safety of Rivaroxiban has been evaluated in three Phase III studies including 4,571 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. In the population of subjects who have taken at least one dose of Rivaroxiban 10 mg od, a total of 1,191 subjects were included in the knee replacement trial with a scheduled treatmentperiod of about 2 weeks and 3,380 subjects included in the total hip replacement trials with a

treatment duration and for treatment period until Day 12 ± 2. The most frequently reported treatment-emergent adverse reactions in both treatment groups during both treatment periods were gastrointestinal disorders, in particular nausea; procedural complications such as post- operative anaemia; and investigations, in particular related to liver function tests. The adverse events and adverse reactions are presented within each system organ class; and should be interpreted within the surgical setting. Adverse events and adverse reactions as reported by theinvestigators in the three Phase III studies are listed in Table 6 below by system organ class (inMedDRA).

RECORD 1-3 trials were similar in study design and patient population, the dose regimen tested was rivaroxaban 10 mg od compare to enoxaparin 40 mg od.

Table 6: Treatment-emergent adverse events (AE) ≥1% (regardless of causality) and treatment emergent adverse reactions (ADR) starting after initiation of rivaroxaban, as reported by the investigators in patients in three Phase III studies (RECORD 1 to 3) 11354, 11357, 11356

	XARELTO (10 mg od) N = 4657		Enoxaparin/Placebo (40 mg od) N = 4692	
System Organ Class Medical Entity / Preferred Term	AE	ADR	AE	ADR
Blood and lymphatic system disorders Anaemia (incl. respective lab parameters)		54 (1.16%)		55 (1.17%)
Cardiac disorders				
Hypertension	77 (1.65%)		86 (1.83%)	
Hypotension	244 (5.24%)		238 (5.07%)	
Tachycardia	74 (1.59%)		71 (1.51%)	
Procedural hypotension	47 (1.01%)		34 (0.72%)	
Endocrine disorders				
Hyperglycaemia	43 (0.92%)		53 (1.13%)	
Gastrointestinal disorders				
Nausea	517 (11.10%)	69 (1.48%)	519 (11.06%)	86 (1.83%)
Constipation	318 (6.83%)		335 (7.14%)	
Diarrhoea	106 (2.28%)		137 (2.92%)	
Dyspepsia	42 (0.90%)		51 (1.09%)	
GI and abdominal pain	89 (1.91%)		93 (1.98%)	
Vomiting	452 (9.71%)		482 (10.27%)	
General disorders and administration site conditions				
Feeling unwell	92 (1.98%)		81 (1.73%)	
Fever	430 (9.23%)		444 (9.46%)	
Headache	108 (2.32%)		108 (2.30%)	
Peripheral Oedema	202 (4.34%)		168 (3.58%)	
Unspecific pain	285 (6.12%)		295 (6.29%)	
Infections and infestations				

	Rivaroxiban (10 mg od) N = 4657		Enoxaparin/Placebo (40 mg od) N = 4692	
System Organ Class Medical Entity / Preferred Term	**AE**	**ADR**	**AE**	**ADR**
Urinary tract infection	82 (1.76%)		90 (1.92%)	
Injury, Poisoning and Procedural Complications				
Arthralgia	65 (1.40%)		81 (1.73%)	
Post procedural haemorrhage (incl. postoperative anaemia and wound haemorrhage)	292 (6.27%)	123 (2.64%)	279 (5.95%)	109 (2.32%)
Wound healing complications	199 (4.27%)		161 (3.43%)	
Investigations				
Increase in blood alkaline phosphatase	38 (0.82%)		57 (1.21%)	
Increase in transaminases (incl. ALT increase, AST increase)	150 (3.22%)	102 (2.19%)	208 (4.43%)	137 (2.92%)
Increased gamma-glutamyltransferase	84 (1.80%)	56 (1.20%)	126 (2.69%)	73 (1.56%)
Increased lactate dehydrogenase	45 (0.97%)		56 (1.19%)	
Musculoskeletal and connective tissue disorders				
Increased muscle tone and cramping	62 (1.33%)		39 (0.83%)	
Nervous system disorders				
Dizziness	156 (3.35%)		144 (3.07%)	
Sleep disorders	191 (4.10%)		196 (4.18%)	
Syncope	60 (1.29%)		33 (0.70%)	
Renal and urinary disorders				
Urinary retention	84 (1.80%)		84 (1.79%)	
Respiratory, thoracic and mediastinal disorders				

	Rivaroxiban (10 mg od) N = 4657		Enoxaparin/Placebo (40 mg od) N = 4692	
System Organ Class Medical Entity / Preferred Term	AE	ADR	AE	ADR
Dyspnoea	49 (1.05%)		58 (1.24%)	
Skin and subcutaneous tissue disorders				
Pruritus	110 (2.36%)		87 (1.85%)	
Rash	60 (1.29%)		57 (1.21%)	
Unspecific blistering	68 (1.46%)		43 (0.92%)	
Social circumstances				
Anxiety reaction	52 (1.12%)		39 (0.83%)	
Vascular disorders				
Haemorrhage	67 (1.44%)		72 (1.53%)	
Thrombocytosis	79 (1.70%)		87 (1.85%)	
Deep vein thrombosis	198 (4.25%)		363 (7.74%)	

Category	**Conditions / Symptoms**
Blood and Lymphatic System Disorders	Thrombocytosis (including increased platelet count)
Cardiac Disorders	Tachycardia
Gastrointestinal Disorders	Constipation, diarrhea, abdominal and gastrointestinal pain (including upper abdominal pain, stomach discomfort), dyspepsia (including epigastric discomfort), dry mouth, vomiting
General Disorders and Administration Site Conditions	Localized edema, decreased general strength and energy (including fatigue, asthenia), feeling unwell (including malaise)
Hepatobiliary Disorders	Hepatic impairment
Immune System Disorders	Dermatitis allergic
Injury, Poisoning, and Procedural Complications	Wound secretion
Investigations	Increased lipase, increased amylase, increased blood bilirubin, increased LDH, increased alkaline phosphatase, increased

Category	Conditions / Symptoms
	conjugated bilirubin (with or without increased ALT)
Musculoskeletal, Connective Tissue, and Bone Disorders	Pain in extremity
Nervous System Disorders	Dizziness, headache, syncope (including loss of consciousness)
Renal and Urinary Disorders	Renal impairment (including increased blood creatinine, increased blood urea)
Skin and Subcutaneous Tissue Disorders	Pruritus (including rare cases of generalized pruritus), rash, urticaria (including rare cases of generalized urticaria), contusion
Vascular Disorders	Hypotension (including blood pressure decrease, procedural hypotension), hematoma (including rare cases of muscle hemorrhage), gastrointestinal tract hemorrhage (including gingival bleeding, rectal hemorrhage, hematemesis), urogenital tract hemorrhage, nosebleed

Treatment of DVT, PE and Prevention of Recurrent VTE The safety of Rivaroxaban has been evaluated in three Phase III trials with 4,556 patients treated up to 21 months and exposed to either 15 mg Rivaroxabantwice daily for 3 weeks followed by 20 mg once daily (EINSTEIN DVT and EINSTEIN PE) or 20 mg once daily (EINSTEIN Extension).Treatment-emergent drug-related adverse events were reported by 28.5% ofrivaroxaban treated subjects and by 28.6% of enoxaparin/VKA treated subjects (pooled studies 11702 DVT and 11702 PE). The respective incidence rates for the study 11899 were 16% rivaroxaban vs. 11% placebo.Themost common treatment-emergent adverse reactions reported in patients validfor safety analysis in the three Phase III studies for DVT or PE treatment and prevention of recurrent VTE are presented in Table 7.

Table 7: Treatment-Emergent Adverse Reactions grouped by System Organ Class occurring in > 1% of any treatment group – pooled EINSTEIN-DVT and EINSTEIN-PE studies (11702-DVT and 11702-PE) and EINSTEIN-Extension (11899) (patients valid for safety analysis)

	Pooled EINSTEIN-DVT and EINSTEIN-PE		EINSTEIN-Extension	
System Organ Class /PT MedDRA	**XARELTO (N = 4130) n (%)**	**ENOXAPARIN /VKA (N = 4116) n (%)**	**XARELTO (N = 598) n (%)**	**Placebo (N = 590) n (%)**
Blood and lymphatic system disorders				
Anaemia	84 (2.03)	62 (1.51)	4 (0.67)	2 (0.34)
Cardiac disorder				
Tachycardia	55 (1.33)	43 (1.04)	2 (0.33)	0
Eye disorders				
Conjunctival haemorrhage	12 (0.70)	21 (1.23)	6 (1.00)	0
Gastrointestinal disorders				
Gingival bleeding	93 (2.25)	104 (2.53)	11 (1.84)	2 (0.34)
Rectal haemorrhage	90 (2.18)	56 (1.36)	4 (0.67)	4 (0.68)
Abdominal pain	69 (1.67)	53 (1.29)	2 (0.33)	7 (1.19)
Abdominal pain upper	71 (1.72)	50 (1.21)	10 (1.67)	1 (0.17)
Constipation	187 (4.53)	174 (4.23)	6 (1.00)	5 (0.85)
Diarrhoea	179 (4.33)	164 (3.98)	7 (1.17)	8 (1.36)
Dyspepsia	60 (1.45)	54 (1.31)	8 (1.34)	4 (0.68)
Nausea	153 (3.70)	160 (3.89)	7 (1.17)	6 (1.02)
Vomiting	69 (1.67)	96 (2.33)	3 (0.50)	6 (1.02)
General disorders and administration site conditions				
Pyrexia	111 (2.69)	108 (2.62)	5 (0.84)	7 (1.19)
Oedema peripheral	128 (3.10)	135 (3.28)	13 (2.17)	17 (2.88)
Asthenia	61 (1.48)	60 (1.46)	4 (0.67)	6 (1.02)
Fatigue	90 (2.18)	68 (1.65)	6 (1.00)	3 (0.51)
Injury, poisoning and post procedural complications				
Wound haemorrhage	59 (1.43)	65 (1.58)	11 (1.84)	7 (1.19)
Contusion	145 (3.51)	197 (4.79)	19 (3.18)	16 (2.71)
Subcutaneous haematoma	44 (1.07)	61 (1.48)	0	2 (0.34)
Investigations				

]

	Pooled EINSTEIN-DVT and EINSTEIN-PE		EINSTEIN-Extension	
System Organ Class /PT MedDRA	**Rivaroxiban (N = 4130) n (%)**	**ENOXAPARIN /VKA (N = 4116) n (%)**	**Rivaroxiban (N = 598) n (%)**	**Placebo (N = 590) n (%)**
Alanine aminotransferase increased	72 (1.74)	129 (3.13)	2 (0.33)	4 (0.68)
Aspartate aminotransferase increased	32 (0.77)	44 (1.07)	4 (0.67)	3 (0.51)
Musculoskeletal, connective tissue and bone disorders				
Pain in extremity	230 (5.57)	221 (5.37)	29 (4.85)	35 (5.93)
Nervous system disorders				
Headache	284 (6.88)	242 (5.88)	18 (3.01)	15 (2.54)
Dizziness	102 (2.47)	108 (2.62)	6 (1.00)	8 (1.36)
Renal and urinary disorders				
Haematuria	111 (2.69)	113 (2.75)	13 (2.17)	2 (0.34)
Reproductive system and breast disorders				
Menorrhagia#	122 (2.95)	64 (1.55)	5 (0.84)	2 (0.34)
Vaginal haemorrhage	54 (1.31)	23 (0.56)	1 (0.17)	5 (0.85)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	307 (7.43)	271 (6.58)	24 (4.01)	11 (1.86)
Haemoptysis	100 (2.42)	98 (2.38)	1 (0.17)	1 (0.17)
Skin and subcutaneous tissue disorders				
Pruritus	83 (2.01)	58 (1.41)	2 (0.33)	2 (0.34)
Rash	97 (2.35)	89 (2.16)	5 (0.84)	7 (1.19)
Vascular disorders				
Haematoma	91 (2.20)	150 (3.64)	7 (1.17)	8 (1.36)

observed as very common for rivaroxaban in women < 55 years in Study 11702

Less frequent ADRs ≥ 0.1% to <1% unless otherwise specified (pooled EINSTEINDVT, EINSTEIN-PE and EINSTEIN-Extension) Eye disorders eye haemorrhage

Gastrointestinal Disorders:	anal haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, lower gastrointestinal haemorrhage, melaena, lip haemorrhage, mouth haemorrhage, tongue haemorrhage, abdominal discomfort, abdominal pain lower, dry mouth
General Disorders and Administration Site Conditions:	feeling abnormal (≥ 0.01% to < 0.1%), malaise
Hepatobiliary Disorders:	hepatic impairment, jaundice (≥ 0.01% to < 0.1%)
Immune System Disorders:	hypersensitivity
Injury, poisoning and post procedural complications:	operative haemorrhage, post procedural haemorrhage, traumatic haematoma, traumatic haemorrhage, subdural haematoma (≥ 0.01% to < 0.1%)
Investigations:	haemoglobin decreased, liver function test abnormal, hepatic enzyme increased, transaminases increased, blood bilirubin increased, bilirubin conjugated increased (with or without concomitant increase of ALT), gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood amylase increased, occul blood positive
Nervous System Disorders:	syncope, cerebellar haemorrhage (≥ 0.01% to < 0.1%), cerebral haemorrhage (≥ 0.01% to < 0.1%), haemorrhag intracranial (≥ 0.01% to < 0.1%), haemorrhagic transformation stroke (≥ 0.01% to < 0.1%)
Reproductive system and breast disorders:	menometrorrhagia (≥ 0.01% to < 0.1%), metrorrhagia
Skin and Subcutaneous Tissue Disorders:	urticaria, ecchymosis, skin haemorrhage, drug eruption, dermatitis allergic, pruritus generalised
Vascular Disorders:	hypotension

Prevention of stroke and systemic embolism in patients with atrial fibrillation In the pivotal double-blind ROCKET AF study, a total of 14,264 unique subjects with nonvalvular atrial fibrillation who were at risk for stroke and non-CNS systemic embolism were randomly assigned to treatment with either rivaroxaban (7,131 subjects) or warfarin (7,133 subjects) in 45 countries. Patients received Rivaroxaban20 mg orally once daily (15 mgorally once daily in patients with moderate (CrCl: 30-49 mL/min) renal impairment) orwarfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The safety population included subjects who were uniquely randomised and took at least 1 dose of study medication. In total, 14,236 subjects were included in the safety population (used for the safety analyses), with 7,111 and 7,125 subjects in rivaroxaban and warfarin groups, respectively. The median time on treatment was 19 months and overall treatment duration was up to 41 months. The mean duration of Rivaroxabantreatment exposure was 572 days. The treatment-emergent adverse reactions reported in patients valid for safety

analysis in ROCKET AF are presented in Table 8.

Table 8: Incidence of treatment-emergent adverse reactions grouped by System Organ Class occurring > 1% of any treatment group – Subjects Valid for Safety Analysis – ROCKET AF SN11630

MedDRA System Organ Class Preferred Term	Rivaroxaban (N = 7111) n (%)	Warfarin (N = 7125) n (%)
Blood and lymphatic system disorders		
Anaemia	219 (3.08)	143 (2.01)
Eye disorders		
Conjunctival haemorrhage	104 (1.46)	151 (2.12)
Gastrointestinal disorders		
Diarrhoea	379 (5.33)	397 (5.57)
Gingival bleeding	263 (3.70)	155 (2.18)
Nausea	194 (2.73)	153 (2.15)
Constipation	163 (2.29)	153 (2.15)
Rectal haemorrhage	149 (2.10)	102 (1.43)
Abdominal pain upper	127 (1.79)	120 (1.68)
Vomiting	114 (1.60)	111 (1.56)
Dyspepsia	111 (1.56)	91 (1.28)
Abdominal pain	107 (1.50)	118 (1.66)
Gastrointestinal haemorrhage	100 (1.41)	70 (0.98)
General disorders and administration site conditions		
Oedema peripheral	435 (6.12)	444 (6.23)
Fatigue	223 (3.14)	221 (3.10)
Asthenia	125 (1.76)	106 (1.49)
Pyrexia	72 (1.01)	87 (1.22)
Injury, poisoning and post procedural complications		
Contusion	196 (2.76)	291 (4.08)
Investigations		
Alanine amino transferase increased	144 (2.03)	112 (1.57)

MedDRA System Organ Class Preferred Term	Rivaroxaban (N = 7111) n (%)	Warfarin (N = 7125) n (%)
Musculoskeletal, connective tissue and bone disorders		
Pain in extremity	191 (2.69)	208 (2.92)
Nervous system disorders		
Dizziness	433 (6.09)	449 (6.30)
Headache	324 (4.56)	363 (5.09)
Syncope	130 (1.83)	108 (1.52)
Renal and urinary disorders		
Haematuria	296 (4.16)	242 (3.40)
Respiratory tract disorders		
Epistaxis	721 (10.14)	609 (8.55)
Haemoptysis	99 (1.39)	100 (1.40)
Skin and subcutaneous tissue disorders		
Ecchymosis	159 (2.24)	234 (3.28)
Pruritus	120 (1.69)	118 (1.66)
Rash	112 (1.58)	129 (1.81)
Vascular disorders		
Haematoma	216 (3.04)	330 (4.63)
Hypotension	141 (1.98)	130 (1.82)

Less frequent ADRs ≥ 0.1% to < 1% unless otherwise specified – ROCKET AF

Cardiac disorders:	Tachycardia
Eye disorders:	Eye haemorrhage, vitreous haemorrhage
Gastrointestinal Disorders:	Melaena, upper gastrointestinal haemorrhage, haemorrhoidal haemorrhage, haematochezia, mouth haemorrhage, lower gastrointestinal haemorrhage, anal haemorrhage, gastric ulcer haemorrhage, gastritis haemorrhagic, gastric haemorrhage, haematemesis, abdominal discomfort, abdominal pain lower, dry mouth

General Disorders and Administration Site Conditions:	Malaise
Hepatobiliary Disorders:	Hepatic impairment, hyperbilirubinaemia, jaundice (≥ 0.01% to <0.1%)
Immune System Disorders:	Hypersensitivity
Injury, Poisoning, and Procedural Complications:	Post procedural haemorrhage, wound haemorrhage, traumatic haematoma, incision site haemorrhage, subdural haematoma, subcutaneous haematoma, periorbital haematoma
Investigations:	Haemoglobin decreased, haematocrit decreased, blood bilirubin increased, liver function test abnormal, aspartate aminotransferas increased, hepatic enzyme increased, blood urine present, creatinine renal clearance decreased, blood creatinine increased, blood urea increased, blood alkaline phosphatase increased, lipase increased, bilirubin conjugated increased (with or without concomitant increase of ALT) (≥ 0.01% to <0.1%)
Renal and urinary disorders:	Renal impairment
Reproductive system disorders:	Vaginal haemorrhage, metrorrhagia
Musculoskeletal, Connective Tissue, and Bone Disorders:	Haemarthrosis, muscle haemorrhage (≥0.01% to <0.1%)
Nervous system disorders:	Loss of consciousness, haemorrhagic stroke, haemorrhage intracranial
Skin and Subcutaneous Tissue Disorders:	Dermatitis allergic, rash pruritic, rash erythemateous, rash generalized, pruritus generalized, urticaria, skin haemorrhage
Vascular disorders:	Haemorrhage, bleeding varicose vein

IN OTHER CLINICAL STUDIES, VASCULAR PSEUDOANEURYSM FORMATION

FOLLOWING PERCUTANEOUS INTERVENTION HAS BEEN REPORTED. Refer to CLINICAL TRIALS section for safety study in patients with non-valvular atrial fibrillation undergoing PCI.

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 Hepatobiliary disorders: cholestasis, hepatitis (including hepatocellular injury) Blood and lymphatic system disorders: thrombocytopaenia, agranulocytosis Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS)

https://pv.pharmacyboardkenya.org/

4.9 OVERDOSE

Overdose following administration of Rivaroxaban tablets may lead to haemorrhagic complications due to its pharmacodynamic properties.
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 or above.
A specific antidote antagonising the pharmacological effect of rivaroxaban is not available. For all overdoses, the mainstay of treatment is supportive and symptomatic care. Activated charcoal may reduce absorption of the drug if given within 8 hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.
Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antithrombotic agent

Mechanism of action
Rivaroxaban is a highly selective direct Factor Xa inhibitor with oral bioavailability. Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1,000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of Factor Xa activity was observed in humans.

Pharmacodynamic effects

Dose dependent inhibition of Factor Xa activity was observed in humans.
Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin 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.

Table 9: 5/95 percentiles for PT (Neoplastin®) after tablet intake

Dosage	VTE Prevention in total hip and knee replacement		DVT and PE Treatment and prevention of recurrent DVT and PE		Stroke Prevention in Atrial Fibrillation*
	10 mg	15 mg bid	20 mg od	15 mg od	20 mg od
5/95 percentiles for PT (Neoplastin®) 2 – 4 hours after tablet intake (seconds)	13 – 25	17 - 32	15 – 30	10 – 50	14 – 40

od = once daily, bid = twice daily

*measurements of 5/95 percentiles for PT were recorded 1 – 4 hours after tablet intake

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. Anti-Factor Xa activity is influenced by rivaroxaban (see Section 4.4). There is no need for monitoring of coagulation parameters while using Rivaroxaban tablets. No QTc prolonging effect was observed with rivaroxaban.

Clinical trials

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbsThe RECORD clinical program was designed to demonstrate the efficacy ofrivaroxaban for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind Phase III clinical studies, known as the RECORD-program.

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

Table 10: Patient demographics – RECORD studies

Study	No of patients	N (%) / Sex		Mean age ± SD (years)
RECORD 1 (THR)	2,209 rivaroxaban 2,224 enoxaparin	1,971 (44.5)/ male	2,462 (55.5)/ female	63.2 ± 11.4
RECORD 2 (THR)	1,228 rivaroxaban 1,229 enoxaparin	1,139 (46)/ male	1,318 (54)/ female	61.5 ± 13.4
RECORD 3 (TKR)	1,220 rivaroxaban 1,239 enoxaparin	781 (31.8)/ male	1,678 (68.2)/ female	67.6 ± 9.0

The respective studies were heterogeneous with respect to their composition of participating countries (centres from Europe, North and South America, Asia and Australia). Men and women of 18 years or older scheduled for hip or knee replacement surgery could be enrolled provided that they had no active or high risk ofbleeding or other conditions contraindicating treatment with low-molecular weight heparin, no significant liver disease, were not pregnant or breastfeeding, or were not using HIV protease inhibitors. In all three pivotal studies, rivaroxaban 10 mg once dailystarted not earlier than 6 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours preoperatively.

The primary efficacy analysis in all studies was based on stratified (by geographical region) risk difference between rivaroxaban and enoxaparin and corresponding 2- sided 95% confidence intervals. Efficacy was assessed in two steps; first a noninferiority test was performed based on the per protocol population. Since noninferiority was shown, a pre- specified superiority analysis was performed subsequently based on the modified ITT population. In all three phase III studies (see Table 11) rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE or death) and major VTE (proximal DVT, non-fatal PE or VTE-related death), the prespecified primary and major secondary efficacy endpoints. The results were clinically meaningful and statistically significant. Relative risk reductions in total VTE were 49% (RECORD 3) and 70% (RECORD 1) in comparison to enoxaparin and 79% (RECORD 2) in comparison to enoxaparin/placebo. Furthermore, in all three studiesthe 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. 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-authorisation, noninterventional, open- label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban 10 mg with other standard-of- care (82% received LMWH) pharmacological thromboprophylaxis in a 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). This noninterventionalstudy confirmed the efficacy and safety results seen in the RECORD program.

Table 11: Efficacy and safety results from Phase III RECORD (VTE Prevention in THR, TKR)

Study Population	RECORD 1			RECORD 2			RECORD 3		
	4541 patients undergoing total hip replacement surgery			2509 patients undergoing total hip replacement surgery			2531 patients undergoing total knee replacement surgery		
Treatment dosage and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days n (%)	Enoxaparin 40 mg od 35 ± 4 days n (%)	p value	Rivaroxaban 10 mg od 35 ± 4 days n (%)	Enoxaparin 40 mg od 12 ± 2 days n (%)	p value	Rivaroxaban 10 mg od 12 ± 2 days n (%)	Enoxaparin 40 mg od 12 ± 2 days n (%)	p value
Total VTE	18 (1.1)	58 (3.7)	<0.001	17 (2.0)	81 (9.3)	<0.001	79 (9.6)	166 (18.9)	<0.001
Major VTE	4 (0.2)	33 (2.0)	<0.001	6 (0.6)	49 (5.1)	<0.001	9 (1.0)	24 (2.6)	0.01
Symptomatic VTE	6 (0.4)	11 (0.7)	--	3 (0.4)	15 (1.7)	--	8 (1.0)	24 (2.7)	--
Major bleedings	6 (0.3)	2 (0.1)	--	1 (0.1)	1 (0.1)	--	7 (0.6)	6 (0.5)	--
PE (non-fatal)	4 (0.3)	1 (<0.1)	--	1 (0.1)	4 (0.5)	--	0 (0.0)	4 (0.5)	--
Death (any cause)	4 (0.3)	4 (0.3)	--	2 (0.2)	6 (0.7)	--	0 (0.0)	2 (0.2)	--
VTE related death	0 (0.0)	1 (<0.1)	--	0 (0.0)	1 (0.1)	--	0 (0.0)	0 (0.0)	--

n = number of events; (%) = percentage

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

The ROCKET-AF clinical program was designed to demonstrate the efficacy of Rivaroxabanfor the prevention of stroke and systemic embolism in patients with non - valvular atrial fibrillation (AF). In the pivotal randomised, double-blind, double-dummy, parallel-group, event-driven, non-inferiority ROCKET-AF study comparing once daily oral rivaroxaban with adjusted-dose oral warfarin, 14,264 patients were assigned either to rivaroxaban 20 mg orally once daily (15 mg orally once daily in patients with CrCl 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. Patients included in the trial had non-valvular atrial fibrillation and a history of prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or two or more of the following risk factors without prior stroke:

•age ≥ 75years,

•hypertension,

•heart failure or left ventricular ejection fraction ≤ 35%, or

• diabetes mellitus

The mean age of patients was 71 years with 44% > 75 years. The population was60% male, 83% Caucasian, 13% Asian and 4% other. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less). A few patients were on clopidogrel and 11.4 % on class III antiarrhythmics including amiodarone. The study included patients with co morbidities e.g. 55% secondary prevention population (prior stroke/ TIA/ Systemic embolism), hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. Patients with various degrees of renal impairment were included in the study, seeTable 12 for details.

Table 12: Baseline patient numbers for creatinine clearance groups

CrCl mL/min (degree of renal impairment)	rivaroxaban n = 7123	warfarin n = 7124
<30 (severe)	4 (0.1%)	4 (0.1%)
30 - 49 (moderate)	1503 (21.1%)	1475 (20.7%)
50 - 80 (mild)	3321 (46.6%)	3414 (47.9%)
> 80 (normal)	2295 (32.2%)	2231 (31.3%)

Exclusion criteria included:

cardiac related conditions (haemodynamically significant mitral valve stenosis, prosthetic heart valve, planned cardioversion, transient atrial fibrillation caused by reversible disease, known presence of atrial myxoma or left ventricular thrombus and active endocarditis), - haemorrhage risk related conditions (active internal bleeding, major surgical procedure or trauma within 30 days before randomisation, clinically significant gastrointestinal (GI) bleeding within 6 months of randomisation, history of intracranial, intraocular, spinal or atraumatic intra-articular bleeding, chronic haemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm

- planned invasive procedure with potential for uncontrolled bleeding
- sustained uncontrolled hypertension (>180/100 mm Hg) and
- concomitant conditions and therapies listed under Section 4.3 CONTRAINDICATIONS as well as severe disabling stroke (modified Rankin score 4-5) or any stroke within 14 days, TIA within 3 days, >100 mg acetylsalicylic acid (aspirin), anticipated need for chronic NSAIDs treatment, known HIV infection at the time of screening, significant hepatic impairment or(ALT > 3 x ULN). gastrointestinal (GI) bleeding within 6 months of randomisation, history of intracranial, intraocular, spinal or atraumatic intra-articular bleeding, chronic haemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm)

- planned invasive procedure with potential for uncontrolled bleeding
- sustained uncontrolled hypertension (>180/100 mm Hg) and
- concomitant conditions and therapies listed under Section 4.3 CONTRAINDICATIONS as well as severe disabling stroke (modified Rankin score 4-5) or any stroke within 14 days, TIA within 3 days, >100 mg acetylsalicylic acid (aspirin), anticipated need for chronic NSAIDs treatment, known HIV infection at the time of screening, significant hepatic impairment or(ALT > 3 x ULN).

The Principal Investigators were instructed to dose their patients with warfarin orally once daily, dose-adjusted to a target International

Normalised Ratio [INR] of 2.5 [range 2.0 to 3.0, inclusive]. During the study, INR monitoring (using a Hemosense point of-care INR device [INRatio]) was to occur as clinically indicated but at least every 4 weeks. Unblinded INR measurements were not performed while subjects were on study drug, except in case of a medical emergency. In order to maintain the integrity of the blind, local unblinded INR measurements (i.e., not using the study Hemosense INRatio device) were discouraged for at least 3 days after subjects stopped receiving study drug (after the start of open-label VKA therapy), including when the subject discontinued study medication, or completed the study. After 3 days, VKA dosing was managed using local unblinded INR measurements. Comparative efficacy with standard of care (warfarin) in the double blind clinical trial setting provides evidence that rivaroxaban is as effective as warfarin. There is insufficient experience to determine how Rivaroxabanand warfarin compare when warfarin therapy is well controlled. Unlike some other contemporary trials, these committees did not provide detailed and focused direction to the sites about their handling of individual patient INRs, since onegoal of the trial was to run the study as close to usual care as possible, to maximize generalisability of the final results to standard practice. The primary objective of the study was met, as Rivaroxaban was shown to be noninferior to warfarin in the primary efficacy endpoint, composite of stroke and systemic embolism (HR 0.79, 95% CI 0.66 – 0.96 p < 0.001). As non-inferiority was met,rivaroxaban was tested,as per the pre-specified analysis, for superiority in primary and secondary endpoints. Rivaroxabandemonstrated superiority over warfarin for strokeand systemic embolism in the on treatment, safety population (HR 0.79, 95% CI 0.65– 0.95, p = 0.015). Major secondary endpoints; composite of stroke, systemicembolism and vascular death and composite of stroke, systemic embolism, myocardial infarction (MI) and vascular death were also reduced significantly (seeTable 13)

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 14).

Table 13: Efficacy results from Phase III ROCKET AF (Stroke Prevention in AF)

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7061 Event Rate (100 Pt-yr)#	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7082 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Stroke and Non-CNS Systemic Embolism	189 (1.70)	243 (2.15)	0.79 (0.65-0.95) 0.015*
Stroke, Non-CNS Systemic embolism and Vascular Death	346 (3.11)	410 (3.63)	0.86 (0.74-0.99) 0.034*
Stroke, Non-CNS Systemic Embolism, Vascular Death and MI	433 (3.91)	519 (4.62)	0.85 (0.74-0.96) 0.010*
Stroke	184 (1.65)	221 (1.96)	0.85 (0.70 – 1.03) 0.092
Non-CNS Systemic Embolism	5 (0.04)	22 (0.19)	0.23 (0.09 – 0.61) 0.003**
All-cause Mortality	208 (1.87)	250 (2.21)	0.85 (0.70 – 1.02) 0.073[a]

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)

Number of events per 100 patient years of follow up

* Statistically significant at 0.025 (one-sided) for non-inferiority and 0.05 (two-sided) for superiority in favour of rivaroxaban

** Statistically significant at nominal alpha = 0.05 (two-sided) a p value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio

Table 14: Safety results from Phase III ROCKET AF (Stroke Prevention in AF)

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7111 Event Rate (100 Pt-yr) #	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7125 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Major and Non-major Clinically Relevant bleeding events	1475 (14.91)	1449 (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*

Study Population	Patients with non-valvular atrial fibrillation (AF) ^		
Treatment Dosage	Rivaroxaban 20 mg orally od (15 mg orally od in patients with CrCl 30 to 49 mL/min) N=7111 Event Rate (100 Pt-yr) #	Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) N=7125 Event Rate (100 Pt-yr) #	Hazard Ratio (95% CI) p-value
Intracranial haemorrhage	55 (0.49)	84 (0.75)	0.67 (0.47 – 0.93) 0.019*
Haemoglobin drop	305 (2.77)	254 (2.26)	1.22 (1.03 – 1.44) 0.019*
Transfusion of 2 or more units of packed red blood cells or whole blood.	183 (1.65)	149 (1.32)	1.25 (1.01 – 1.55) 0.044*
Non-major Clinically Relevant bleeding events	1185 (11.80)	1151 (11.37)	1.04 (0.96 – 1.13) 0.345

^ Safety population, on treatment = All ITT subjects who take at least 1 dose of study medication after randomisation during double-blind treatment period or within 2 days after discontinuation (site 042012 was excluded for efficacy analysis)# Number of events per 100 patient years of follow up

* Statistically significant at nominal alpha = 0.05 (two-sided)

In addition to the phase III ROCKET AF study, a prospective, single-arm, postauthorisation, non-interventional, open-label cohort study (XANTUS) with centraloutcome adjudication including thromboembolic events and major bleeding has been conducted, wherein 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism under real-world conditions (safety analysis set n= 6,784). The mean CHADS2 score was 2.0 compared to a mean CHADS2 score of 3.5 in ROCKET AF. 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 from routine clinical practice are consistent with the results observed inthe ROCKET AF study.

Cardioversion

A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1,504 patients (oral anticoagulant naïve and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversionto compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the preventionof cardiovascular events. Transoesophageal echocardiogram-guided (TOE-guided) (1-5 days of pre-treatment) or conventional cardioversion (at least three weeks of pretreatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, MI and cardiovasculardeath) 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 the VKAs treatment groups in the setting of cardioversion.

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and a VKA regimen. PIONEER AF-PCI was designed and powered to assess safety but was not powered to compare efficacy between the rivaroxaban regimens and a VKA regimen. Data on efficacy (including thromboembolic events) in this population are limited. In this 12-month safety study, Group 1 of 696 patients received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 – 49 mL/min) plus single antiplatelet (P2Y12 inhibitor). Group 2 of 706 patients 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 of 697 patients received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA. Patients with a history of stroke or TIA were excluded from the trial. The primary safety endpoint, clinically significant bleeding events [a composite of TIMI major bleeding, TIMI minor bleeding and Bleeding Requiring Medical Attention (BRMA)], occurred in 109 (15.7%) and in 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 reduction in the risk of clinically significant bleeding events was primarily a result of significantly fewer BRMA events in patients on the rivaroxaban regimen. The secondary efficacy endpoints composite of cardiovascular events (CV death, MI,or stroke) occurred in 41(5.9%) and in 36(5.1%) and 36 (5.2%) subjects in the Group 1,Group 2 and Group 3, respectively

Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and prevention of recurrent DVT and PE.

The EINSTEIN clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrent DVT and PE. Over 12,800 patients were studied in four randomised controlled Phase III clinical studies (EINSTEIN DVT, EINSTEIN PE and EINSTEIN Extension) and additionally a predefined analysis of the pooled EINSTEIN DVT and EINSTEIN PE studies was conducted (see Table 18). The overall combined treatment duration in all studies was up to 21 months. 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, 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 the composite of the primary efficacy outcome, MI, ischemic stroke, or non-CNS

systemic embolism.

EINSTEIN DVT and EINSTEIN PE studies

In the EINSTEIN DVT and EINSTEIN PE, open label, randomised, event driven noninferiority studies, 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE; 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. Concomitant conditions listed under Section 4.3 CONTRAINDICATIONS as well as subjects who had significant liver disease or ALT > 3 x ULN, bacterial endocarditis, VKA treatment indicated other than DVT and/or PE were excluded from these studies. Based on the clinical judgement of the investigator, the treatment duration was up to 12 months in both studies, assigned prior to randomisation. For the initial 3 week treatment of acute DVT and acute PE, 15 mg of Rivaroxaban was administered twice daily. This was followed by 20 mg of Rivaroxabanonce daily.Patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) were treated with the same dose as patients with creatinine clearance above 50 mL/min (i.e. 15 mg twice daily forthe first three weeks and 20 mg once daily from day 22 onwards). The comparator combination with vitamin K antagonist treatment until the prothrombin time/international normalised ratio (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.

After randomisation, subjects allocated to the comparator arm received enoxaparintwice daily for at least 5 days in combination with VKA (overlap 4 to 5 days) andcontinued with VKAonly afterthe INR had been ≥ 2 for two consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs. Warfarin and acenocoumarol were to be started not later than 48 hours after randomisation. VKA dosages were individually titrated and adjusted to achieve atarget INR of 2.5 and maintain the INR within the therapeutic range (range 2.0-3.0) foreither 3, 6 or 12 months. The INR had to be measured initially every 2 to 3 days, andat least once monthly once stable. Each centre had to specify before study startwhich VKA compound (warfarin or acenocoumarol) would be used during the study.

In the ITT analysis of EINSTEIN DVT, subjects were comparable between treatmentgroups. About 57% of subjects were male. The race of about 77% of subjects wasdescribed as white, about 13% as Asian, and about 2% as black. Age ranged from18-95 years in the rivaroxaban and from 18-97 years in the enoxaparin/VKA group,with a mean of approximately 56 years in both groups. Mean body weight was about82 kg, with ranges from 33 to 193 kg.

In the ITT analysis of EINSTEIN PE, subjects were comparable between treatment groups. 54.1% and 51.7% were men in the rivaroxaban and enoxaparin / VKA groups respectively. The race of about 66% of subjects was described as white. Age ranged from 18 to 97 years, with a mean of approximately 58 years in both treatment groups. Mean body weight was about 83 kg, ranging from 35 to 220 kg.

Table 15: Baseline patient numbers for creatinine clearance groups in EINSTEIN DVT and EINSTEIN PE

	EINSTEIN DVT		EINSTEIN PE	
Creatinine clearance (mL/min)	Rivaroxaban n = 1525	Enox/VKA n = 1571	Rivaroxaban n = 2419	Enox/VKA n = 2413
< 30 mL/min (severe)	6 (0.3%)	9 (0.5%)	4 (0.2%)	2 (< 0.1%)
30 - 49 mL/min (moderate)	115 (6.6%)	120 (7.0%)	207 (8.6%)	191 (7.9%)
50 - 80 mL/min (mild)	393 (22.7%)	399 (23.2%)	637 (26.3%)	593 (24.6%)
> 80 mL/min (normal)	1193 (68.9%)	1170 (68.1%)	1555 (64.3%)	1617 (67.0%)

EINSTEIN-DVT (see Table 16) met its principal objective, demonstrating that Rivaroxabanwas non -inferior to enoxaparin/VKA for the primary outcome of symptomatic recurrent VTE (HR of 0.68 [95% CI = 0.44 – 1.04], p <0.001). The prespecified test for superiority was not statistically significant (p = 0.0764). The incidence rates for the principal safety outcome (major or clinically relevant non-major bleeding events), as well as the secondary safety outcome (major bleeding events),were similar for both groups (HR of 0.97 [95% CI = 0.76 – 1.22], p = 0.77 and HR of 0.65 [95% CI = 0.33 – 1.30), p = 0.21, respectively). The pre-defined secondary outcome of net clinical benefit, (the composite of the primary efficacy outcome and major bleeding events), was reported with a HR of 0.67 ([95% CI = 0.47 – 0.95], p = 0.03) in favour of Rivaroxaban.

The relative efficacy and safety findings were consistent regardless of pre-treatment (none, LMWH, unfractionated heparin or fondaparinux) as well as among the 3, 6 and 12-month durations. In terms of other secondary outcomes, vascular events occurredin 12 patients (0.7%) in the Rivaroxabanarm and 14 patients (0.8%) in the enoxaparin/VKA group (HR of 0.79 [95% CI = 0.36 – 1.71], p = 0.55), and total

mortality accounted for 38 (2.2%) vs. 49 (2.9%) patients in the Rivaroxabanvs.enoxaparin/VKA arms, respectively (p =0.06).

Table 16: Efficacy and safety results from Phase III EINSTEIN DVT (DVT treatment)

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment Dosage and Duration	Rivaroxaban 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N=1731	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N=1718
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%)

Study Population	3,449 patients with symptomatic acute deep vein thrombosis	
Treatment Dosage and Duration	Rivaroxaban 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N=1731	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N=1718
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major bleeding events	14 (0.8%)	20 (1.2%)
All-cause Mortality	38 (2.2%)	49 (2.9%)

*p: < 0.0001 (non-inferiority), 0.076 (superiority), HR: 0.680 (0.443 - 1.042) In the EINSTEIN PE study (see Table 17) rivaroxaban was demonstrated to be noninferior to

enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for noninferiority); hazard ratio: 1.12 (0.75 - 1.68)). The pre-specified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.85 ((95% CI: 0.63 - 1.14), nominal p value p=0.275).

The incidence rate for the primary safety outcome (major or clinically relevant nonmajor bleeding events) was 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 hazard ratio 0.49 (95% CI: 0.31 - 0.79; p-value for superiority 0.0032).

Table 17: Efficacy and safety results from Phase III EINSTEIN PE (PE treatment)

Study Population	4,832 patients with an acute symptomatic PE	
Treatment dosage and duration	Rivaroxiban 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N = 2419	Enoxaparin for 5 days followed by VKA 3, 6 or 12 months N = 2413
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 bleeding events	26 (1.1%)	52 (2.2%)

* p<0.0026 (non-inferiority); hazard ratio: 1.12 (0.75 - 1.68)

A prespecified pooled analysis of the outcome of the EINSTEIN DVT and PE studies was conducted (see Table 18)

Table 18: 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 dosage and duration	Rivaroxaban 15 mg BID for 3 weeks followed by 20 mg OD 3, 6 or 12 months N = 4,150	Enoxaparin for 5 days followed by VKA 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 bleeding events	40 (1.0%)	72 (1.7%)

* p<0.001 (non-inferiority); hazard ratio: 0.89 (0.66 - 1.19)

EINSTEIN Extension study

EINSTEIN Extension, a double blind, randomised, event driven superiority study included 1,197 patients with confirmed symptomatic DVT or PE. Rivaroxaban20 mg once daily was compared with placebo for an additional 6 to 12 months in patients who had completed initial treatment for DVT or PE for 6 to 14 months; where clinical uncertainty with respect to the need for continued anticoagulation existed. Patients with moderate renal impairment (creatinine clearance 30 - 49 mL/min) were treatedwith the same dose as patients with creatinine clearance above 50 mL/min (i.e. 20 mg once daily). The treatment duration, assigned prior to randomisation,

was based onthe clinical judgement of the investigator.
In the EINSTEIN-Extension study (see Table 19), Rivaroxabanwas superior to placebo for the primary efficacy outcome with a HR of 0.18 [95% CI = 0.09 – 0.39], p<0.001(i.e. a relative risk reduction of 82%). For the principal safety outcome (major bleeding events) there was no significant difference between patients treated with Rivaroxabancompared to placebo (p= 0.11). Therefore, the pre-defined secondary outcome of net clinical benefit, defined as the composite of the primary efficacy outcome and major bleeding events, was reported with a HR of 0.28 ([95% CI = 0.15 – 0.53], p<0.001) in favour of Rivaroxaban.

Table 19: Efficacy and safety results from Phase III EINSTEIN EXTENSION (Prevention of recurrent DVT and PE)

Study Population	**1,197 patients continued treatment and prevention of recurrent venous thromboembolism**	
Treatment Dosage and Duration	Rivaroxaban 20 mg OD 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%)
All-cause mortality	38 (2.2%)	49 (2.9%)

* p<0.0001 (superiority), HR: 0.185 (0.087 - 0.393)

In terms of other secondary outcomes, vascular events occurred in 3 patients in the Rivaroxabanarm and 4 patients in the placebo group (HR of 0.74 [95% CI = 0.17 -3.3],p=0.69) and total mortality accounted for 1 (0.2%) vs. 2 (0.3%) of patients in the Rivaroxaban vs placebo arms, respectively.

EINSTEIN CHOICE study

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 randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and Rivaroxaban 10 mg once daily were compared with 100mg acetylsalicylic acid once daily.

In the EINSTEIN CHOICE study Rivaroxaban 20 mg and 10 mg were both superior to 100mg acetylsalicylic acid for the primary efficacy outcome. The secondary efficacy outcome was reduced when comparing Rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. The principal safety outcome (major bleeding events) was similar for patients treated with Rivaroxaban and 10 mg once daily compared to 100 mg acetylsalicylic acid. The secondary safety outcome (non-major bleeding associated with treatment cessation of more than 14 days) was similar when comparing Rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. Outcomes wereconsistent across the patients with provoked and unprovoked VTE (see Table 20).

Table 20: Efficacy and safety results from phase III EINSTEIN CHOICE

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dosage	Rivaroxaban 20 mg od N=1,107	Rivaroxaban 10 mg od N=1,127	ASA 100 mg od 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%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Symptomatic recurrent VTE or major clinical bleeding (net clinical benefit)	23 (2.1%)+#	17 (1.5%)++#	53 (4.7%)

* p<0.001(superiority) Rivaroxiban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20 -0.59)

** p<0.001 (superiority)Rivaroxiban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)

*** The primary endpoint (Symptomatic recurrent VTE) was the first occurrence of the event. The individual component of the primary efficacy was the incidence rates up to the end of the intended treatment duration.
# The symptomatic recurrent VTE or major clinical bleeding (net clinical benefit) was the first occurrence of the event.

In addition to the phase III EINSTEIN program, 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 under real-world conditions. In the safety analysis set (n=4,768), 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 hazard ratios comparing rivaroxaban and standard-of-care for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40-1.50, p=0.44), 0.91 (95% CI 0.54-1.54, p=0.72) and 0.51 (95% CI 0.24-1.07, p=0.074), respectively.
Rivaroxaban showed similar safety and efficacy compared to standard anticoagulation.

These results in patients who were observed in routine clinical practice are consistent with those observed in the EINSTEIN DVT study.

Coronary artery disease (CAD) and/or peripheral artery disease (PAD): Clinical efficacy and safety
The phase III double-blind, randomised COMPASS study (27,395 patients,

78.0% male, 22.0% female) demonstrated the efficacy and safety of Rivaroxiban for the prevention of a composite of CV death, MI, stroke in patients with CAD and/or PAD. Patients were followed for a median of 23 months and maximum of 3.9 years.

In the COMPASS trial, 27,395 patients were randomly assigned to one of three antithrombotic treatment groups:Rivaroxiban2.5 mg twice daily in combination with aspirin 100 mg once daily,Rivaroxiban5mg twice daily or to aspirin 100 mg once daily in a 1:1:1 fashion. Patients with established CAD and/or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] <60 mL per minute, heart failure or non-lacunar ischemic stroke ≥ 1 month earlier). Exclusion criteria included patients in need of dual antiplatelet, other nonaspirin antiplatelet, or oral anticoagulant therapies, as well as patients with a history of ischaemic, non-lacunar stroke within 1 month, any history of haemorrhagic or lacunar strokeor patients with eGFR < 15 mL/min.

The COMPASS Study was terminated early per recommendation of the Data Safety Monitoring Board (DSMB) after the first interim analysis. DSMB recommended that the antithrombotic study treatment arms were to be stopped early because the log-rank test statistic for one of the primary efficacy comparisons had crossed the pre-specified boundary consistently over 3 months. The intended average study duration was approximately 3-4 years. The actual (mean) treatment duration was 1.69 years for the Rivaroxaban regimens (2.5mg bid/ASA 100mg od or 5mg bid) and 1.71 years for the ASA 100mg od regimen, respectively.

The mean age was 68 years and 21% of the subject population were ≥ 75 years. Of the patients included, 91% had CAD, 27% had PAD, and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior myocardial infarction, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/percutaneous coronary intervention (PCI) and 26% had a history of coronary artery bypass grafting (CABG) prior to the study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty (PTA), 26% had asymptomatic carotid artery stenosis >50% and 5% had limb or foot amputation for arterial vascular disease.

Relative to aspirin 100 mg, Rivaroxiban2.5mg twice daily in combination with aspirin 100 mg once daily was superior in the reduction of the primary composite outcome of stroke, myocardial infarction or cardiovascular death. The benefit was observed early with a constant treatment effect over the entire treatment period (see Table 21 and Figure 1). The composite secondary outcomes (composites of coronary heart disease death, or cardiovascular death, with myocardial infarction, ischaemic stroke, and acute limb ischaemia) as well as all-cause mortality were reduced (see Table 21: Efficacy results from phase III COMPASS)

A post-hoc analysis of the individual component acute limb ischemia (ALI) showed a reduction for the combination of rivaroxaban 2.5 mg bid and ASA 100 mg od with regard to maintaining limb circulation and function in subjects with atherosclerosis. For ALI, superiorityof Rivaroxaban 2.5 mg bid/ASA 100 mg od (n=22) when compared with ASA 100 mg od (n=40) was shown by a HR of 0.55 (95% CI 0.32-0.92, p-value = 0.02093), corresponding toa RRR of 45%. Amputations for cardiovascular reasons (15 vs 31 events) were also reduced

(HR 0.48; 95% CI 0.26-0.89, p=0.01755).
The composite outcome of stroke, myocardial infarction and all-cause mortality was also reduced (HR 0.79; 95% CI 0.70-0.88; p=0.00005, post-hoc analysis).
There was a significant 1.7-fold increase of the primary safety outcome (modified ISTH major bleeding events) in patients treated with Rivaroxiban 2.5 mg twice daily in combination with aspirin 100 mg once daily compared to patients who received aspirin 100 mg (see Table 22). For the primary efficacy outcome, the observed benefit of Rivaroxiban 2.5 mg twice daily plus ASA 100 mg once daily compared with ASA 100 mg once daily was HR=0.89 (95% CI 0.7-1.1) in patients ≥75 years (incidence: 6.3% vs 7.0%) and HR=0.70 (95% CI 0.6-0.8) in patients <75 years (3.6% vs 5.0%). For modified ISTH major bleeding, the observed risk increase was HR=2.12 (95% CI 1.5-3.0) in patients ≥75 years (5.2% vs 2.5%) and HR=1.53 (95% CI 1.2-1.9) in patients <75 years (2.6% vs 1.7%).
The prespecified composite outcome for net clinical benefit (cardiovascular death, myocardial infarction, stroke, fatal or symptomatic critical-organ bleeding events) was reduced (see Table 20). The results in patients with PAD, CAD, and both CAD and PAD were consistent with the overall efficacy and safety results (see Table 23).
The estimated cumulative incidence risk of major bleeding events is higher with Rivaroxiban 2.5 mg twice daily in combination with aspirin 100 mg daily compared to aspirin 100 mg soon after, indicating that more major bleeding events occur early. After one year the difference in cumulative incidence risk is nearly constant.
In the ITT population, 3.8% of patients with a prior history (not within one month of enrolment) of ischaemic, non lacunar stroke were included. The median time since stroke was 5 years. For these patients the reduction of major cardiovascular events (stroke, myocardial infarction and cardiovascular death), and the increase of major bleeding (net clinical benefit HR 0.64; 95% CI 0.4-1.0) were consistent with the overall population (see Section 4 CLINICAL PARTICULARS).
Relative to aspirin 100 mg, XARELTO 5 mg twice daily alone did not significantly reduce the primary composite efficacy outcome of stroke, myocardial infarction or cardiovascular death (HR 0.90; 95% CI 0.79-1.03; p=0.11490). The incidence rates for the primary safety outcome (modified ISTH major bleeding events) were significantly increased in patients treated with XARELTO 5 mg twice daily compared with patients who received aspirin 100 mg daily (HR 1.51; 95% CI 1.25-1.84; p=0.00003)

Table 21: Efficacy results from phase III COMPASS

Study Population	**Patients with CAD and/or PAD** [a)]		
Treatment Dosage	**Rivaroxiban 2.5 mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)**[b)]	**aspirin 100 mg od N=9126 n (Cum. risk %)**[b)]	**Hazard Ratio (95% CI) p-value** [c)]
Stroke, MI or CV death	379 (5.2%)	496 (7.2%)	0.76 (0.66;0.86) p = 0.00004*
- Stroke	83 (1.2%)	142 (2.2%)	0.58 (0.44;0.76) p = 0.00006
- MI	178 (2.5%)	205 (2.9%)	0.86 (0.70;1.05) p = 0.14458
- CV death	160 (2.2%)	203 (2.9%)	0.78 (0.64;0.96) p = 0.02053
Coronary heart disease death, MI, ischaemic stroke, acute limb ischaemia	329 (4.5%)	450 (6.6%)	0.72 (0.63;0.83) p = 0.00001
- Coronary heart disease death#	86 (1.2%)	117 (1.6%)	0.73 (0.55;0.96) p = 0.02611
- Ischaemic stroke	64 (0.9%)	125 (2.0%)	0.51 (0.38;0.69) p = 0.00001
- Acute limb ischaemia**	22 (0.3%)	40 (0.6%)	0.55 (0.32;0.92) p = 0.02093
- CV death, MI, ischaemic stroke, acute limb ischaemia	389 (5.3%)	516 (7.5%)	0.74 (0.65;0.85) p = 0.00001
- All-cause mortality	313 (4.5%)	378 (5.6%)	0.82 (0.71;0.96) p = 0.01062

Relative to aspirin 100 mg, Rivaroxiban 5 mg twice daily alone did not significantly reduce the primary composite efficacy outcome of stroke, myocardial infarction or cardiovascular death (HR 0.90; 95% CI 0.79-1.03; p=0.11490). The incidence rates for the primary safety outcome (modified ISTH major bleeding events) were significantly increased in patients treated with Rivaroxiban 5 mg twice daily compared with patients who received aspirin 100 mg daily (HR 1.51; 95% CI 1.25-1.84; p=0.00003)

Study Population	Patients with CAD and/or PAD [a]		
Treatment Dosage	Rivaroxiban 2.5 mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)[b]	aspirin 100 mg od N=9126 n (Cum. risk %)[b]	Hazard Ratio (95% CI) p-value [c]
- Stroke, MI or all-cause mortality	526 (7.4%)	659 (9.6%)	0.79 (0.70;0.88) p = 0.00005
- CV death, MI, stroke, fatal or symptomatic critical-organ bleeding events (net clinical benefit)	431 (5.9%)	534 (7.7%)	0.80 (0.70;0.91) p = 0.00052

a) intention to treat analysis set, primary analyses

b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. aspirin 100 mg; Log-Rank p-value

* The reduction in the primary efficacy outcome was statistically superior. Nominal p-value significant at p<0.05.

CHD coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure

** Acute limb ischaemia is defined as limb-threatening ischaemia leading to an acute vascular angioplasty/stent, or amputation) bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction; CV: cardiovascular

Table 22: Safety results from phase III COMPASS

Study Population	Patients with CAD and/or PAD [a]		
Treatment Dosage	Rivaroxiban 2.5 mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)[b]	aspirin 100 mg od N=9126 n (Cum.risk %)[b]	Hazard Ratio (95 % CI) p-value [c]
Modified ISTH major bleeding*	288 (3.9%)	170 (2.5%)	1.70 (1.40;2.05) p < 0.00001
- Fatal bleeding event	15 (0.2%)	10 (0.2%)	1.49 (0.67;3.33) p = 0.32164
- Symptomatic bleeding in critical organ (non-fatal)	63 (0.9%)	49 (0.7%)	1.28 (0.88;1.86) p = 0.19679
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	10 (0.1%)	8 (0.1%)	1.24 (0.49;3.14) p = 0.65119

Study Population	Patients with CAD and/or PAD [a]		
Treatment Dosage	**Rivaroxiban 2.5mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)[b]**	**aspirin 100 mg od N=9126 n (Cum.risk %)[b]**	**Hazard Ratio (95 % CI) p-value [c]**
- Bleeding leading to hospitalisation (non-fatal, not in critical organ, not requiring reoperation)	208 (2.9%)	109 (1.6%)	1.91 (1.51;2.41) p<0.00001
- With overnight stay	172 (2.3%)	90 (1.3%)	1.91 (1.48;2.46) p < 0.00001
- Without overnight stay	36 (0.5%)	21 (0.3%)	1.70 (0.99;2.92) p = 0.04983
Major gastrointestinal bleeding	140 (2.0%)	65 (1.1%)	2.15 (1.60;2.89) p < 0.00001
Major intracranial bleeding	28 (0.4%)	24 (0.3%)	1.16 (0.67;2.00) p = 0.59858

a) intention-to-treat analysis set, primary analyses

b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. aspirin 100 mg; Log-Rank p-value

bid: twice daily; od: once daily; CI: confidence interval;

* Modified ISTH major bleeding defined as:

(1) Fatal bleeding or

(2) Symptomatic bleeding in a critical area or organ, such as intraarticular, intramuscular with compartment syndrome, intraspinal, intracranial, intraocular, respiratory, pericardial, liver, pancreas, retroperitoneal, adrenal gland or kidney; or bleeding into the surgical site requiring reoperation or
(3) Bleeding leading to hospitalisation (Includes with and without overnight stay. Based on attending A&E but not necessarily being admitted.

Table 23 : Efficacy and safety results from phase III COMPASS in subpopulation with CAD, PAD, or both CAD and PAD

Study Population	**Patients with CAD and/or PAD by subgroups [a)]**		
Treatment Dosage	**Rivaroxiban 2.5 mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)[b)]**	**aspirin 100 mg od N=9126 n (Cum. risk %)[b)]**	**Hazard Ratio (95% CI) p-value [c)]**
Patients with CAD	**N=8313[d)]**	**N=8261[d)]**	
Stroke, MI, or CV death	347 (5.2%)	460 (7.3%)	0.74 (0.65;0.86) p = 0.00003
Modified ISTH major bleeding	263 (4.0%)	158 (2.5%)	1.66 (1.37;2.03) p < 0.00001
Stroke MI, CV death, fatal or symptomatic critical organ bleeding	392 (5.8%)	494 (7.8%)	0.78 (0.69;0.90) 0.00032
Patients with PAD	**N=2492 [d)]**	**N=2504 (100%)[d)]**	
Stroke, MI, or CV death	126 (6.6%)	174 (10.3%)	0.72 (0.57;0.90) p = 0.00466
Modified ISTH major bleeding	77 (4.0%)	48 (2.5%)	1.61 (1.12;2.31) p = 0.00890
Stroke MI, CV death, fatal or symptomatic critical organ bleeding	140 (7.1%)	185 (10.7%)	0.75 (0.60;0.94) p = 0.01072
Patients with CAD and PAD	**N=1656**	**N=1641**	
Stroke, MI, or CV death	94 (7.2%)	138 (12.0%)	0.67 (0.52;0.87) p = 0.00262
Modified ISTH major bleeding	52 (4.3%)	36 (2.6%)	1.43 (0.93;2.19) p = 0.09819

Study Population	Patients with CAD and/or PAD by subgroups [a]		
Treatment Dosage	Rivaroxiban 2.5 mg bid in combination with aspirin 100 mg od, N=9152 n (Cum. risk %)[b]	aspirin 100 mg od N=9126 n (Cum. risk %)[b]	Hazard Ratio (95% CI) p-value [c]
Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	101 (7.5%)	145 (12.3%)	0.68 (0.53;0.88) p = 0.00327

a) intention to treat analysis set, primary analyses.

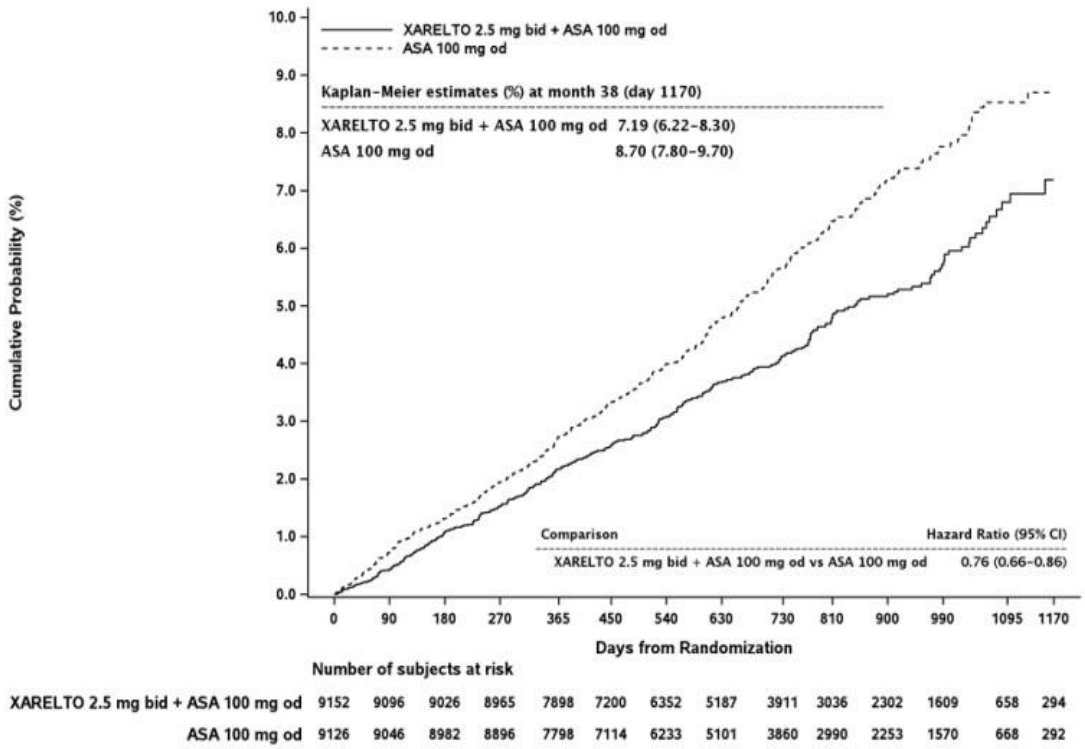
b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. aspirin 100 mg; Log-Rank p-value

bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction, CV: cardiovascular

d) Patients could have more than one clinical diagnosis indicating either CAD and/or PAD. bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction, CV: cardiovascular

Figure 1: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS



bid: twice daily; od: once daily; CI: confidence interval

Patients with high risk triple positive antiphospholipidsyndrome
In an investigator sponsored randomised open-label multicentre 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 trial 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. Fifty nine patients were randomised to rivaroxaban 20mg (15 mg for patients with creatinine clearance between 30 up to 49 mL/min) and 61 to warfarin (INR 2.0-3.0).

Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic stroke and 3 myocardial infarction). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (Cmax) appearing 2 – 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is high (80- 100%) for the 10 mg dose irrespective of fasting/fed conditions. Under fed conditions Rivaroxaban tablets 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. Oral bioavailability of Rivaroxaban tablets Rivaroxaban tablets 20 mg tablet is reduced to 66% under fasting conditions. When Rivaroxaban tablets 20 mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions. This indicates almost complete absorption and high oral bioavailability.

Rivaroxaban tablets 10 mg tablets can be taken with or without food. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose (see Section 4.2).

Rivaroxaban tablets Rivaroxaban tablets 15 mg and 20 mg tablets should be taken with food (see Section 4.2). The data regarding food effect is limited.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30% to 40%, apart from the day of surgery and the following day when variability in exposure is high (70%) in patients who underwent hip or knee replacement. Absorption of rivaroxaban is dependent on the site of drug release in the GI 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 drug is released in the distal small intestine, or ascending colon. In case of administration of Rivaroxaban tablets through nasogastric/enteral tube, avoid administration of rivaroxaban distal to the stomach which can result in reduced absorption and related drug exposure.

Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple sauce, 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 human is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 L.

Metabolism

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation. Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Based on in vitro investigations rivaroxaban is a substrate of the transporter proteins P-gp (P glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present.

Excretion

Of the approximately 2/3 that undergoes metabolic degradation, half is then eliminated renallyand the other half eliminated by the faecal route. The other 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active secretion.With a systemic clearance of about 10 L/h rivaroxaban can be classified as a lowclearance drug. Elimination of rivaroxaban from plasma occurred with terminal halflives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Gender / Elderly (above 65 years)

Whilst elderly patients exhibited higher plasma concentrations than younger patients with AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance, no dose adjustment is necessary (see Section).There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients (see Section 4.2)

Different weight categories

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary (see Section 4.2). **Children and adolescents (from birth to 18 years)**

No data are available for this patient population (see Section 4.2). Rivaroxaban tablets is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

Interethnic differences

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics andpharmacodynamics (see Section 4.2).

Hepatic impairment

The critical aspect of liver impairment is the reduced synthesis of normal coagulationfactors in the liver, which is captured by only one of the five clinical/biochemical measurements composing the Child-Pugh classification system. The bleeding risk in patients may not clearly correlate with this classification scheme. Therefore, the decision to treat patients with an anticoagulant should be made independently of

the Child-Pugh classification. Cirrhotic patients with mild hepatic impairment (classified as Child-Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. No relevant difference in pharmacodynamics properties was observed between these groups. In cirrhotic patients with moderate hepatic impairment (classified as ChildPugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2.6-fold. There are no data in patients with severe hepatic impairment. Theinhibition of FXa activity was increased by a factor of 2.6 as compared to healthy volunteers;prolongation of PT was similarly increased by a factor of 2.1.

The global clotting test PT assesses the extrinsic pathway that comprises of coagulation Factors VII, X, V, II, and I, which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT. The elevated PT at baseline and a significantly altered sensitivity in anti-coagulant activity towards rivaroxaban plasma exposure (increase in slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients with moderate hepatic impairment indicate the decreased ability of the liver to synthesize coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk inthis patient group.
Therefore, Rivaroxaban tablets is contraindicated in patients with significant hepatic disease(including moderate and severe hepatic impairment, i.e. Child-Pugh B and C) which is associated with coagulopathy leading to a clinically relevant bleeding risk. No data are available for severe hepatic impairment (Child-Pugh C patients) (see Section 4.2).
Rivaroxaban tablets may be used with caution in cirrhotic patients with moderate hepaticimpairment if it is not associated with coagulopathy.

Renal impairment

Rivaroxaban exposure was inversely correlated to the decrease in renal function, as assessed via creatinine clearance (CrCl) measurements. In individuals with mild (creatinine clearance 50 - 80 mL/min), moderate (creatinine clearance 30 – 49 mL/min) and severe (creatinineclearance 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (Section 4.2).
Corresponding increases in pharmacodynamic effects were more pronounced (see Section 4.2 and Section 4.4) in individuals with mild, moderate or severe renal impairment; the overall inhibition of FXa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers. Prolongation of PT was similarly increased by a factor of 1.3,
2.2 and 2.4 respectively.

There are no data in patients with CrCl < 15 mL/min. Use is contraindicated in patients with creatinine clearance < 15 mL/min (see Section 4.3). Rivaroxaban tablets 10 mg is to be used with caution in patients with severe renal impairment creatinine clearance 15 – 29 mL/min. Rivaroxaban tabletsRivaroxaban tablets 15 mg and 20 mg are contraindicated in patients

with CrCl < 30 mL/min (see Section 4.2 , Section 4.3 and Section 4.4).Due to the underlying disease, patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. The increased exposure to rivaroxaban further increases the risk of bleeding in these patients. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.If there is a suspicion of renal impairment, the degree of renal impairment must be determined accurately. Caution must be exercised when renal function estimates are based on eGFR. In clinical trials, renal function was determined using the calculated creatinine clearance, using the Cockcroft-Gault Formula as follows:

For serum creatinine concentration in mg/ 100 mL:

$$\text{Creatinine Clearance mL / min} = \frac{(140\text{-age [years]}) \times \text{wight [kg]}}{72 \times \text{serum creatinine [mg / 100kg mL]} \times (0.85 \text{ for women})}$$

For serum creatinine concentration in µmol/L:

$$\text{Creatinine Clearance [mL / min]} = \frac{1.23 \times (140\text{-age [years]}) \times \text{wight [kg]}}{\text{serum creatinine [µmol/L]}}$$

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Testing was performed by oral dosing for 2 years at up to 60 mg/kg/day reaching unbound plasma rivaroxaban exposure levels similar to humans (mice) or up to 3.6- fold higher (rats) than in humans. Rivaroxaban showed no carcinogenic potential in either species.

6. PHARMACEUTCAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate
Microcrystalline cellulose

Croscarmellose sodium
Sodium Lauryl Sulphate
Hydroxypropyl
Methylcellulose
Purified Water *
Croscarmellose sodium
Magnesium Stearate
Opadry brown

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.

POM	**PP**	**NS3**	**Schedule 2**

6.5 Nature and contents of container

Blister pack (1x10's, 3x10's and 10x10's)hdpe container (30's, 200 & 1000's) not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Name:	MSN Laboratories Private Limited**,**
Address:	MSN HOUSE, Plot No.: C-24, Industrial Estate,Sanathnagar, Hyderabad 500 018, Telangana.
Country:	India

Manufacturing site address:

Name: MSN Laboratories Private Limited

Address: **Formulations Division, Unit-II, Sy. No. 1277 & 1319 to 1324, Nandigama (Village & Mandal), Rangareddy District, Telangana, Pin Code: 509 228.**

Country: **India**

8. Marketing authorization number
H2024/CTD10438/21081

9. Date of first registration
27/02/2024

10. Date of revision of the text
November 2024