1 PRODUCT NAME® (strength pharmaceutical form)

RIVOXA® (rivaroxaban) 2.5 mg film-coated tablets

RIVOXA® (rivaroxaban) 10 mg film-coated tablets

RIVOXA® (rivaroxaban) 15 mg film-coated tablets

RIVOXA® (rivaroxaban) 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of RIVOXA

- 2.5 mg contains 2.5 mg of rivaroxaban
- 10 mg contains 10 mg of rivaroxaban
- 15 mg contains 15 mg of rivaroxaban
- 20 mg contains 20 mg of rivaroxaban

Excipient with known effect

Each film-coated tablet of RIVOXA 2.5 mg, 10mg, 15mg and 20mg contains sugars, as lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated (immediate release) tablet.

RIVOXA 2.5 mg – Light yellow, circular, biconvex film coated tablets, debossed with "123" on one side and “2.5” on other side.

RIVOXA 10 mg – Light pink, circular, biconvex film coated tablets, debossed with "124" on one side and “10” on other side.

RIVOXA 15 mg – Maroon, circular, biconvex film coated tablets, debossed with "125" on one side and “15” on other side.

RIVOXA 20 mg – Dark Maroon, circular, biconvex film coated tablets, debossed with "126" on one side and “20” on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RIVOXA is indicated for:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and pulmonary embolism (see section 4.4 for haemodynamically unstable PE patients).

RIVOXA, in combination with aspirin, is indicated for:

- The 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)

4.2 Dose and method of administration

4.2.1 Dose

4.2.1.1 VTE Prevention in total hip and knee replacement

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

The initial dose should be taken 6 - 10 hours after surgery provided that haemostasis has been established.

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.

4.2.1.2 Stroke Prevention in Atrial Fibrillation

The recommended dose is 20 mg once daily.

For patients with severe and moderate renal impairment (Creatinine clearance: 15 – 49 mL/min), one 15 mg tablet of RIVOXA should be taken once daily. Due to limited clinical data caution should be taken in patients with severe renal impairment (Creatinine clearance 15 - 29 mL/min).

Therapy with RIVOXA should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding.

Cardioversion

RIVOXA can be initiated or continued in patients who may require cardioversion.

For TOE-guided cardioversion in patients not previously treated with anticoagulants, RIVOXA treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see Section 5.1 Pharmacodynamic properties and Section 5.2 Pharmacokinetic properties).

4.2.1.3 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 RIVOXA **twice daily** for the first three weeks followed by 20 mg RIVOXA **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 RIVOXA should be taken twice daily.

After the initial 3 weeks treatment RIVOXA 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 RIVOXA once daily may be considered.

RIVOXA 15 mg tablets and RIVOXA 20 mg tablets should be taken with food.

4.2.1.4 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 RIVOXA twice daily in combination with a daily dose of 100 mg aspirin.

In patients with CAD and/or PAD, RIVOXA 2.5 mg twice daily is not indicated in combination with dual antiplatelet therapy (see Section 5.1 Pharmacodynamic properties).

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.

4.2.1.5 Special Populations

Hepatic impairment

RIVOXA 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 Contraindications). No dose adjustment is necessary in patients with other hepatic diseases (see Section 5.2 Pharmacokinetic properties).

Limited clinical data in patients with moderate hepatic impairment (Child-Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child-Pugh C) (see Section 4.3 Contraindications and Section 5.2 Pharmacokinetic properties).

Renal impairment

Prior to commencing treatment with RIVOXA, an accurate assessment of renal function should be undertaken, especially if there is any suspicion that the person may have a degree of renal impairment (see Section 5.2 Pharmacokinetic properties).

No clinical data are available for patients with (CrCl < 15 mL/min) or patients on dialysis. Therefore, use of RIVOXA is contraindicated in this patient population (see Section 4.3 Contraindications). RIVOXA should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Please refer to 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 in total 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="2">10 mg once daily</td><td rowspan="2">20 mg once daily</td><td rowspan="4">15 mg twice daily for 3 weeks, followed by 20 mg once daily for 6 to 12 months, then maintain 20 mg once daily or consider* 10 mg once daily</td><td rowspan="4">2.5 mg RIVOXA twice daily with 100 mg aspirin once daily.</td></tr>
<tr><td>Mild
50 – 80 mL/min</td></tr>
<tr><td>Moderate
30 – 49 mL/min</td><td rowspan="2">10 mg once daily</td><td rowspan="2">15 mg once daily</td></tr>
<tr><td>Severe
15 – 29 mL/min
(Use with caution)</td></tr>
<tr><td>Severe
< 15 mL/min</td><td colspan="4">RIVOXA is contraindicated</td></tr>
</table>

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

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).

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).

Children and adolescents

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

Ethnic differences

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

4.2.1.6 Switch from Vitamin K Antagonists (VKA) to Rivaroxaban

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and rivaroxaban 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 therapy should be initiated once the INR is ≤ 2.5.

The INR is not a valid measure for the anticoagulant activity of rivaroxaban, 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, INR values will be elevated after the intake of rivaroxaban but this is not indicative of the anticoagulant effect of rivaroxaban (see section 4.5).

4.2.1.7 Switch from Parenteral Anticoagulants to Rivaroxaban

For patients currently receiving a parenteral anticoagulant, start rivaroxaban 0 to 2 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).

4.2.1.8 Switch from Rivaroxaban to Parenteral Anticoagulants

Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time that the next rivaroxaban dose would be taken.

4.2.1.9 Switch from Rivaroxaban to VKAs

There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Limited clinical trial data are available to guide the process whereby patients are converted from rivaroxaban to VKAs.

Continuous adequate anticoagulation should be ensured during transition to an alternate anticoagulant. In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. It should be noted that rivaroxaban 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 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 and VKA, INR should be tested just prior to the next dose of rivaroxaban (not earlier than 24 hours after the previous dose). Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

4.2.1.10 Missed dose

It is essential to adhere to the dosage schedule provided.

- RIVOXA 2.5 mg **twice** daily with 100mg aspirin once a day.
- RIVOXA 10 mg, 15 mg or 20 mg tablets taken **once** a day:

  If a dose is missed, the patient should take RIVOXA 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.

- RIVOXA 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.

4.2.2 Method of administration

RIVOXA 2.5 mg tablets and RIVOXA 10 mg tablets may be taken with or without food (see section 5.2).
RIVOXA 15 mg tablets and RIVOXA 20 mg tablets should be taken with food (see section 5.2).

For patients who are unable to swallow whole tablets; RIVOXA 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 RIVOXA 15 mg or 20 mg tablets, the dose should be immediately followed by food.
The crushed RIVOXA 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 RIVOXA. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed RIVOXA 15 mg or 20 mg tablets, the dose should be immediately 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 tablet to PVC or silicone nasogastric (NG) tubing.

4.3 Contraindications

Rivaroxaban is contraindicated in patients:

- who are hypersensitive to the active substance or to any of the excipients listed in section 6.1
- 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 and Section 5.2)
- undergoing dialysis or patients with severe renal impairment with a creatinine clearance < 15 mL/min for rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg tablets, due to increased plasma levels which may lead to an increased risk of bleeding (see Section 4.4 and Section 5.2)
- 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 4.6.2, see section 4.6.3)

4.4 Special warnings and precautions for use

4.4.1 Haemorrhagic risk

Like other anticoagulants, rivaroxaban increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe rivaroxaban 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, rivaroxaban may be associated with an increased risk of occult or overt bleeding which may result in post haemorrhagic anaemia (see section 4.8). 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 bleeding may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or taking concomitant medications affecting haemostasis.

Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. 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.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.

Patients at high risk of bleeding should not be prescribed rivaroxaban (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).

4.4.2 General haemorrhagic risk factors

Rivaroxaban 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 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

  CAD and/or PAD patients who have experienced an ischemic, non-lacunar stroke within the previous month were not studied. Treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily should be avoided in the first month after 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 Interaction with other medicines and other forms of interaction).

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see Section 4.5 Interaction with other medicines and other forms of interaction).

- CAD symptoms with severe heart failure (LV EF of ≤ 40%) without AF. Study data indicate that such patients may have limited benefit with rivaroxaban (see section 5.1 pharmacodynamic properties – clinical trials).

Bleeding during antithrombotic treatment may unmask underlying yet unknown malignancy, in particular in the gastrointestinal or genitourinary tract. Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis.

4.4.3 Other risk factors

Use in renal impairment

Due to limited clinical data Rivaroxaban 2.5 mg, 10 mg, 15 mg and 20 mg should be used with caution in patients with CrCl 15 – 29 mL/min. Rivaroxaban should not be used in patients with CrCl < 15 mL/min. Patients on dialysis have not been studied. Rivaroxaban should not be used in this population (see Section 4.3, Section 4.2 and Section 5). Rivaroxaban 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 4.5).Physicians should consider the benefit/risk of anticoagulant therapy before administering Rivaroxaban to patients with moderate renal impairment having a creatinine clearance close to the severe renal impairment category (CrCl < 30 mL/min), or in those with a potential to have deterioration of renal function to severe impairment during therapy. Renal function should be followed carefully in these patients. In patients with severe renal impairment (CrCl 15 - 29 mL/min), rivaroxaban plasma levels may be significantly elevated compared to healthy volunteers (1.6-fold on average) which may lead to an increased bleeding risk.

No clinical data are available for patients with creatinine clearance less than 15 mL/min. Therefore, use of rivaroxaban is contraindicated in these patients (see Section 4.3).

Anticoagulant-related nephropathy

There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury. In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).

Use in hepatic impairment

Rivaroxaban 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 may be used in cirrhotic patients with moderate hepatic (Child-Pugh B) impairment if it is not associated with coagulopathy (see Section 5 and Section 4.3).

Strong CYP 3A4 and P-gp inhibitors

Rivaroxaban 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 and Section 4.5 and Table 2). However, fluconazole, a less potent CYP3A4 and P-gp inhibitor has less effect on rivaroxaban and may be co-administered (see section 4.5 and Table 3).

Non-steroidal anti-inflammatory drugs

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

Anticoagulants

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

4.4.4 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 or discontinuation of treatment as appropriate. Rivaroxaban has a terminal half-life between 5 and 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 not expected 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 one of 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, all three procoagulants have demonstrated significant reductions in rivaroxaban-induced bleeding time prolongation in nonclinical studies.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving rivaroxaban.

4.4.5 Surgery and interventions

If an invasive procedure or surgical intervention is required, based on clinical judgement of the physician, Rivaroxaban 10 mg, 15 mg and 20 mg should be stopped at least 24 hours and rivaroxaban 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 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 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 5.2.3).

4.4.6 Patients with prosthetic heart valves

Rivaroxaban is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). In the GALILEO study, patients randomised to rivaroxaban experienced higher rates of all-cause mortality, thromboembolic and bleeding events compared to those randomised to an anti-platelet regimen.

The safety and efficacy of rivaroxaban have not been studied in patients with other prosthetic heart valves or other valve procedures; therefore, there are no data to support that rivaroxaban provides adequate anti-coagulation in those patient populations. Treatment with rivaroxaban is not recommended for these patients.

4.4.7 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 be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

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 anticoagulant effect in each patient is not known.

For 10 mg rivaroxaban, an epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. For 15 mg and 20 mg rivaroxaban, based on general PK characteristics, an epidural catheter should not be removed until at least 2x half-life has elapsed (i.e. at least 18 hours in young adult patients and 26 hours in elderly patients) after the last administration of rivaroxaban (see section 5.2).

The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter.

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

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 20 mg rivaroxaban, therefore the use of indwelling epidural catheters is not recommended in these situations.

4.4.8 Hip fracture surgery

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

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

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

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

The data in this population are limited. There are limited data from a safety study of patients with non-valvular atrial fibrillation, but no previous stroke or TIA, who undergo PCI with stent placement taking rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 – 49 mL/min) plus P2Y12 inhibitor (see CLINICAL TRIALS). Efficacy using this regimen is not established.

4.4.11 Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

4.4.12 Lactose intolerance

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

4.4.13 Information for the Patient

A Consumer Medicine Information leaflet is available. Please advise your patient to read this information carefully.

4.4.14 Paediatric Use

Rivaroxaban 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 sections 4.2 and 5.2).

4.4.15 Use in Elderly

No dose adjustment is required for the elderly (> 65 years of age). It should be taken into consideration that increasing age may be associated with declining renal and hepatic function (see sections 4.3, 4.4. and 5.2).

For prevention of major cardiovascular events in patients with CAD and /or PAD ≥ 75 years of age in combination with aspirin 100 mg once daily:

- Caution should be used in these patients due to their higher bleeding risk. The benefit-risk of the treatment should be individually assessed on a regular basis. (see Section 5.1).

4.4.16 Different Gender and 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 required for these patient populations (see 5.2).

4.4.17 Effect on Laboratory Tests
Rivaxoxaban 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 in a dose-dependent 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 6 (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.

During any conversion period when warfarin and rivaroxaban are overlapped, the pharmacodynamic effects of rivaroxaban can be tested with the anti-Factor Xa activity, PiCT (Prothrombinase-induced Clotting Time), and HepTest® assays, as these tests were not affected by warfarin. Four days after cessation of warfarin and onwards, all tests (including PT, aPTT, anti-Factor Xa activity and ETP) only reflected the effect of rivaroxaban (see sections 4.2 and 5.1).

The INR is not valid to measure 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 to assess rivaroxaban plasma concentrations gravimetrically (ng/mL or µg/L). The pharmacokinetic profile of rivaroxaban has to be taken into account when interpreting results of these tests.

4.4.17 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 5.1.3.5)

4.5 Interaction with other medicines and other forms of interaction

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

CYP Inhibition
Rivaroxaban does not inhibit 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 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 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 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 is contraindicated in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see Section 4.3 Contraindications). 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 Special warnings and precautions for use 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 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 Special warnings and precautions for use). Physicians should consider the benefit/risk of anticoagulant therapy before administering rivaroxaban to patients with moderate renal impairment having a creatinine clearance close to the severe renal impairment category (CrCl < 30 mL/min), or in those with a potential to have deterioration of renal function to severe impairment during therapy. Renal function should be followed carefully in these patients. In patients with severe renal impairment (CrCl 15 - 29 mL/min), rivaroxaban plasma levels may be significantly elevated compared to healthy volunteers (1.6-fold on average) which may lead to an increased bleeding risk.

- ***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 twice daily. Caution should be taken when rivaroxaban 15 and 20 mg tablets are co-administered 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-gp inhibitor Azole-antimycotics e.g. ketoconazole, itraconazole, voriconazole, posaconazole or HIV-protease inhibitors e.g. ritonavir	↑ rivaroxaban	Concomitant treatment with systemic azole-antimycotics or HIV-protease inhibitors 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 C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} 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 C_{max}. This increase, which is close to the magnitude of the normal variability of AUC and C_{max}, is considered to be not clinically relevant.
Moderate CYP3A4 and moderate P-gp inhibitor Erythromycin	↑ rivaroxaban	500 mg tid led to a 1.3-fold increase in mean rivaroxaban steady state AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} 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 RIVOXA may lead to increased 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 RIVOXA may lead to a decreased plasma rivaroxaban concentration.

4.5.2 Pharmacodynamic interactions

Anticoagulants

Enoxaparin

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 RIVOXA 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 Special warnings and precautions for use).

Warfarin

Converting patients from warfarin (INR 2.0 to 3.0) to rivaroxaban 20 mg or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of Factor Xa activity and endogenous thrombin potential were additive. 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 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 (see Section 4.2 Dose and method of administration).

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.

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 Special warnings and precautions for use).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with more pronounced pharmacodynamic response (see Section 4.4 Special warnings and precautions for use).

Platelet aggregation inhibitors

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction (with rivaroxaban 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 bleeding time: 2 to 8 minutes). This increase in the combined treatment group was driven by a subset of patients in whom pronounced prolongations of bleeding times were observed. These prolongations of bleeding time did not correlate to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. For patients on antiplatelet therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases (see Section 4.4 Special warnings and precautions for use).

Selective Serotonin Reuptake Inhibitors or Selective Norepinephrine Reuptake Inhibitors

As with other anticoagulants, the possibility may exist that patients are at increased risk of bleeding 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
RIVOXA 2.5 mg and 10 mg tablets can be taken with or without food (see Section 5.2).

RIVOXA 15 mg and 20 mg tablets should be taken with food (see Section 5.2).

4.5.3 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 bio- availability and pharmacokinetics.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid (see Section 4.4).

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

4.6.2 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 the mother. 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 unbound plasma AUC), while deaths occurred at doses ≥ 40 mg/kg/day (52 times human exposure based on unbound plasma AUC). Changes in placental appearance (course, grained and/or necrotic) were also noted at doses ≥ 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, RIVOXA is contraindicated in pregnancy (see Section 4.3 Contraindications). RIVOXA should be used in women of childbearing potential only with effective contraception.

4.6.3 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, RIVOXA is contraindicated during breast- feeding (see Section 4.3 Contraindications).

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

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 Undesirable effects). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

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
Prevention of venous thromboembolism in medically ill patients	3,997	10 mg	39 days
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively in combination with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source	3,562	15 mg od	24 months
Prevention of symptomatic VTE events and VTE-related deaths for a period of 45 days post-hospital discharge in high-risk medically ill	5,982	10 (or 7.5) mg od	45 days
Reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an episode of decompensated heart failure	2,499	2.5 mg bid combined with ASA 100 mg	42 months (or >1,260 days)

Reducing the cumulative incidence of DVT, PE, and VTE-related death in adult subjects with various cancer types at high risk of developing a VTE	405	10 mg od	6.9 months or (207 days)
Comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimise clinical outcomes	801	10 mg od + low dose ASA / post 90d 10 mg alone	24 months (or 720 days)
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT and PE with 20 mg rivaroxaban once daily	12 months
Prevention of atherothrombotic events in patients after recent revascularisation procedure of the lower limb due to symptomatic PAD	3,256	2.5 mg bid combined with ASA 100 mg	42 months

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

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 years[1].

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

4.8.1.1 Tabulated list of adverse reactions

The frequencies of ADRs reported with rivaroxaban are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

very common (≥ 1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000)

Table 6 – All treatment – emergent adverse reactions reported in patients in Phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS and EINSTIEN DVT/PE/Extension)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Blood and the lymphatic system disorders	Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) *	
Cardiac disorders		Tachycardia	
Eye disorders	Eye haemorrhage (incl. conjunctival haemorrhage)		
Gastrointestinal disorders	Gingival bleeding Gastrointestinal tract haemorrhage (incl. rectal haemorrhage) Gastrointestinal and abdominal pains Dyspepsia Nausea Constipation* Diarrhoea Vomiting *	Dry mouth	
General disorders and administration site conditions	Fever * Oedema peripheral Decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema *
Hepato-biliary disorders		Hepatic impairment	Jaundice
Immune system disorders		Allergic reaction Dermatitis allergic	
Injury, poisoning and postprocedural complications	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) Contusion	Wound secretion *	Vascular pseudoaneurysm^
Investigations	Increase in transaminases	Increase in bilirubin Increase in blood alkaline phosphatase * Increase in LDH * Increase in lipase * Increase in amylase * Increase in GGT *	Bilirubin conjugated increased (with or without concomitant increase of ALT)

Musculoskeletal, connective tissue and bone disorders	Pain in extremity *	Haemarthrosis	Muscle haemorrhage
Nervous system disorders	Dizziness Headache	Cerebral and intracranial haemorrhage Syncope	

System Organ Class (MedDRA)	Common	Uncommon	Rare
Renal and urinary disorders	Urogenital tract haemorrhage (incl. haematuria and menorrhagia #) Renal impairment (incl. blood creatinine increased, blood urea increased) *		
Respiratory tract disorders	Epistaxis Haemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalised pruritus) Rash Ecchymosis Cutaneous and subcutaneous haemorrhage	Urticaria	
Vascular disorders	Hypotension Haematoma		

***observed after major orthopedic surgery of the lower limbs**
#observed in VTE treatment as very common in women <55 years
^observed as uncommon in prevention therapy in Acute Coronary Syndrome (ACS) (following percutaneous intervention)
< ADR term representation is based on MedDRA version 14.1 >

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of a haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Refer to CLINICAL TRIALS section for safety study in patients with non-valvular atrial fibrillation undergoing PCI.

4.8.2 Post-marketing observations

The following adverse reactions have been reported post-marketing in temporal association with the use of RIVOXA. 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

Renal and urinary disorders, Frequency: Not known, Anticoagulant-related nephropathy (see section 4.4).

Injury, poisoning and postprocedural complications: Splenic rupture (In the pooled phase III trials, these events were very rare (< 1/10,000)).

4.8.3 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Overdose following administration of RIVOXA 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

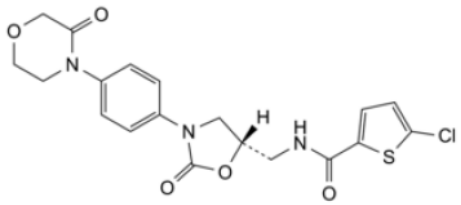
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent, ATC code: B01AF01.

Rivaroxaban is 5-Chloro-N-({(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophene-carboxamide. The empirical formula is C19H18ClN3O5S and molecular weight is 435.89 g / mole.

Rivaroxaban has the following structural formula:



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

5.1.1 Mechanism of action

Rivaroxaban is a highly selective direct acting 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.

5.1.2 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 7: 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 Special warnings and precautions for use).

There is no need for monitoring of coagulation parameters while using rivaroxaban. No QTc prolonging effect was observed with rivaroxaban.

5.1.3 Clinical trials

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

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

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

Table 8: 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 of bleeding or other conditions contraindicating treatment with low-molecular weight heparin, no significant liver disease, were not pregnant or breastfeeding, or were not using HIV protease inhibitors.

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

The primary efficacy analysis in all studies was based on stratified (by geographical region) risk difference between rivaroxaban and enoxaparin and corresponding 2-sided 95% confidence intervals. Efficacy was assessed in two steps; first a non-inferiority test was performed based on the per protocol population. Since non-inferiority was shown, a pre-specified superiority analysis was performed subsequently based on the modified ITT population.

In all three phase III studies (see Table 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 pre-specified primary and major secondary efficacy endpoints. The results were clinically meaningful and statistically significant. Relative risk reductions in total VTE

were 49% (RECORD 3) and 70% (RECORD 1) in comparison to enoxaparin and 79% (RECORD 2) in comparison to enoxaparin/placebo. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non-fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.

The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

Table 9: 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

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, non-interventional, open- label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban 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 non-interventional study confirmed the efficacy and safety results seen in the RECORD program.

In the population of subjects who have taken at least one dose of rivaroxaban 10 mg od, a total of 1191 subjects were included in the knee replacement trial with a scheduled treatment period of about 2 weeks and 3380 subjects included in the total hip replacement trials with a scheduled treatment period of about 5 weeks. The two treatment groups, rivaroxaban and enoxaparin/placebo showed very similar demographic and baseline characteristics.

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

5.1.3.2 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 rivaroxaban for 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 ≥ 75 years,
- 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 was 60% 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, see Table 12 for details.

Table 10: 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).

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 rivaroxaban and 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 one goal 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 non-inferior 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. Rivaroxaban demonstrated superiority over warfarin for stroke and 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, systemic embolism and vascular death and composite of stroke, systemic embolism, myocardial infarction (MI) and vascular death were also reduced significantly (see Table 11).

There were 14,236 subjects in the safety population who were uniquely randomised to rivaroxaban (n = 7111) and warfarin (n = 7125) groups and took at least 1 dose of study medication. The incidence

rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 12).

Table 11: 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 12: 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*
Intracranial	55	84	0.67 (0.47 – 0.93)

haemorrhage	(0.49)	(0.75)	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, post-authorisation, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted, wherein 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and noncentral nervous system (CNS) systemic embolism under real-world conditions (safety analysis set n= 6,703). The mean CHADS2 score was 1.9 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 in the 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 cardioversion to compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the prevention of cardiovascular events. Transoesophageal echocardiogram-guided (TOE-guided) (1-5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, MI and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n=978) and 5 (1.0%) patients in the VKA group (n=492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n=988) and VKA (n=499) groups, respectively (RR 0.76; 95% CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and the VKAs treatment groups in the setting of cardioversion.

5.1.3.3 Safety study in Patients who undergo PCI (percutaneous coronary intervention) with stent placement

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.

5.3.1.4 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 16). 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 non-inferiority 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 RIVOXA was administered twice daily. This was followed by 20 mg of RIVOXA once 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 for the first three weeks and 20 mg once daily from day 22 onwards). The comparator treatment regimen consisted of enoxaparin administered for at least 5 days in 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 enoxaparin twice daily for at least 5 days in combination with VKA (overlap 4 to 5 days) and continued with VKA only after the 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 a target INR of 2.5 and maintain the INR within the therapeutic range (range 2.0-3.0) for either 3, 6 or 12 months. The INR had to be measured initially every 2 to 3 days, and at least once monthly once stable. Each centre had to specify before study start which VKA compound (warfarin or acenocoumarol) would be used during the study.

In the ITT analysis of EINSTEIN DVT, subjects were comparable between treatment groups. About 57% of subjects were male. The race of about 77% of subjects was described as white, about 13% as Asian, and about 2% as black. Age ranged from 18-95 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 about 82 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 13: 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 14) met its principal objective, demonstrating that rivaroxaban was 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 pre-specified 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 occurred in 12 patients (0.7%) in the rivaroxaban arm 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 rivaroxaban vs. enoxaparin/VKA arms, respectively (p = 0.06).

Table 14: 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%)
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 15) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); 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 non-major 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 15: 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	Rivaroxaban 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 16).

Table 16: 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. Rivaroxaban 20 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 treated with 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 on the clinical judgement of the investigator.

In the EINSTEIN-Extension study (see Table 17), Rivaroxaban was 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 rivaroxaban compared 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 17: 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 rivaroxaban arm 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.

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.

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 100 mg acetylsalicylic acid once daily.

In the EINSTEIN CHOICE study rivaroxaban 20 mg and 10 mg were both superior to 100 mg 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 20 mg 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 were consistent across the patients with provoked and unprovoked VTE (see Table 18).

Table 18: 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) Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)**
****p<0.001 (superiority) Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)**
*****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.

5.1.3.5 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 rivaroxaban 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: Rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily, Rivaroxaban 5 mg 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 non-aspirin 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 stroke or 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, Rivaroxaban 2.5 mg 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, superiority of 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 to a 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[2]) in patients treated with rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily compared to patients who received aspirin 100 mg (see Table 20).

[2] 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.)

For the primary efficacy outcome, the observed benefit of rivaroxaban 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 21).

The estimated cumulative incidence risk of major bleeding events is higher with rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg daily compared to aspirin 100 mg soon after starting treatment, 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, rivaroxaban 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 rivaroxaban 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 19: Efficacy results from phase III COMPASS

Study Population	**Patients with CAD and/or PAD** [a)]		
Treatment Dosage	**Rivaroxaban 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
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 intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation)

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

Table 20: Safety results from phase III COMPASS

Study Population	**Patients with CAD and/or PAD** [a)]		
Treatment Dosage	**Rivaroxaban 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
- 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

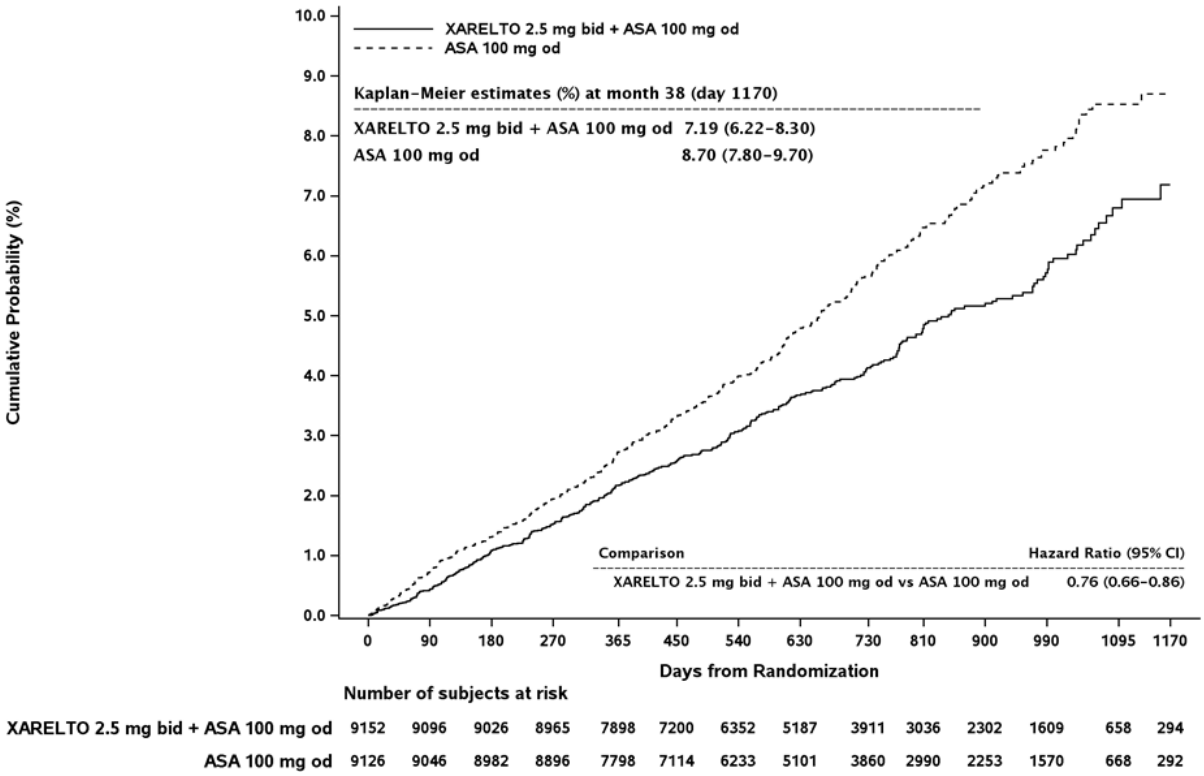
a) intention-to-treat analysis set, primary analyses
b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months
c) vs. aspirin 100 mg; Log-Rank p-value
bid: twice daily; od: once daily; CI: confidence interval;
* Modified ISTH major bleeding defined as:
(1) Fatal bleeding or
(2) Symptomatic 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 21: 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	**Rivaroxaban 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
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.

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

5.1.3.6 CAD with heart failure

The COMMANDER HF study included 5,022 patients with heart failure and significant coronary artery disease (CAD) following a hospitalisation of decompensated heart failure (HF) which were randomly assigned into one of the two treatment groups: rivaroxaban 2.5 mg twice daily (N=2,507) or matching placebo (N=2,515), respectively. The overall median study treatment duration was 504 days.

Patients must have had symptomatic HF for at least 3 months and left ventricular ejection fraction (LVEF) of ≤40% within one year of enrolment. At baseline, the median ejection fraction was 34% (IQR: 28%-38%) and 53% of subjects were NYHA Class III or IV.

The primary efficacy analysis (i.e. composite of all-cause mortality, MI, or stroke) showed no statistically significant difference between the rivaroxaban 2.5 mg bid group and the placebo group with a HR=0.94 (95% CI 0.84 - 1.05), p=0.270. For all-cause mortality, there was no difference between rivaroxaban and placebo in the number of events (event rate per 100 patient-years; 11.41 vs. 11.63, HR: 0.98; 95% CI: 0.87 to 1.10; p=0.743). The event rates for MI per 100 patient-years (rivaroxaban vs placebo) were 2.08 vs 2.52 (HR 0.83; 95% CI: 0.63 to 1.08; p=0.165) and for stroke the event rates per 100 patient-years were 1.08 vs 1.62 (HR: 0.66; 95% CI: 0.47 to 0.95; p=0.023). The principal safety outcome (i.e. composite of fatal bleeding or bleeding into a critical space with a potential for

permanent disability), occurred in 18 (0.7%) patients in the rivaroxaban 2.5 mg twice daily treatment group and in 23 (0.9%) patients in the placebo group, respectively (HR=0.80; 95% CI 0.43 - 1.49; p=0.484). There was a statistically significant increase in ISTH major bleeding in the rivaroxaban group compared with placebo (event rate per 100 patient-years: 2.04 vs 1.21, HR 1.68; 95% CI: 1.18 to 2.39; p=0.003).

In patients with mild and moderate heart failure the treatment effects for the COMPASS study subgroup were similar to those of the entire study population (see above section 'Coronary artery disease (CAD) and/or peripheral artery disease (PAD): Clinical efficacy and safety').

5.1.3.7 Patients with high risk triple positive antiphospholipid syndrome

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

5.2.1 Absorption and Bioavailability

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) 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 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. Oral bioavailability of rivaroxaban 20 mg tablet is reduced to 66% under fasting conditions. When rivaroxaban 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 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 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 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.

5.2.2 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.

5.2.3 Metabolism and Elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the 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.

Rivaroxaban is metabolised via CYP 3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

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

Unchanged rivaroxaban is the most important compound in human plasma with no major or active circulating metabolites being present. With a systemic clearance of about 10 L/h rivaroxaban can be classified as a low-clearance drug. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

5.2.4 Gender / Elderly (above 65 years)

Whilst elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance, no dose adjustment is necessary (see Section 4.2).

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients (see Section 4.2).

5.2.5 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).

5.2.6 Children and adolescents (from birth to 18 years)

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

5.2.7 Interethnic differences

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

5.2.8 Hepatic impairment

The critical aspect of liver impairment is the reduced synthesis of normal coagulation factors 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 Child-Pugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2.6-fold. There are no data in patients with severe hepatic impairment. The inhibition of FXa activity was increased by a factor of 2.6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1.

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

Therefore, rivaroxaban 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 Dose and method of administration). Rivaroxaban may be used with caution in cirrhotic patients with moderate hepatic impairment if it is not associated with coagulopathy.

5.2.9 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 (creatinine clearance 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (see Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

Corresponding increases in pharmacodynamic effects were more pronounced (see Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use) 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 Contraindications). RIVOXA 2.5 mg, 10 mg, 15 mg and 20 mg are to be used with caution in patients with severe renal impairment creatinine clearance 15 – 29 mL/min (see Section 4.2 Dose and method of administration, Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use).

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:

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

For serum creatinine concentration in µmol/L:

$$Creatinine\ Clearance\ [mL/\min] = \frac{1.23 \times (140 - age\ [years]) \times weight\ [kg]}{serum\ creatinine\ [\mu mol/L]} \times (0.85\ for\ women)$$

5.3 Preclinical safety data

5.3.1 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.

5.3.2 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: Microcelac 100, lactose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate

Filmcoat: Opadry yellow, Opadry pink, Opadry brown, purified water.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Store tablets in original pack until required.

6.5 Nature and contents of container

The tablets are packed in PVC/PVDC/Aluminium foil blisters

The 2.5 mg tablets are supplied in packs of 14, 56, 60 and 100 tablets.

The 10 mg tablets are supplied in packs of 3, 10, 15, 30, 100 tablets.

The 15 mg tablets are supplied in packs of 7, 14, 28, 42, 84, 98, 100 tablets.

The 20 mg tablets are supplied in packs of 7, 28, 84, 98, 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

Pharmacor Limited, c/- Wynn Williams
Level 25, Vero Centre, 48 Shortland Street, Auckland Central, Auckland, 1010, New Zealand
Phone: +64 800 172 553 Or 0800 172 553

9 DATE OF FIRST APPROVAL

02/10/2025

10 DATE OF REVISION OF THE TEXT

DD/MM/YY

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**