SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban/Acetylsalicylic acid PharOS 2.5 mg/50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 2.5 mg of rivaroxaban and 50 mg of acetylsalicylic acid.

Excipient with known effect
Each hard capsule contains 315.05 mg lactose, see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

A white opaque hard gelatin capsule of size '00' (23.5 ± 0.4 mm) containing two white to off-white, round, biconvex tablets, blank on both sides and white crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name>, alone or with clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3, 4.4 and 5.1).

<Product name> is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

4.2 Posology and method of administration

Posology

• *ACS*
Patients must take one capsule of <Product name>- twice daily alone, or in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited (see section 5.1).

Treatment with <Product name> should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

• *CAD/PAD*
Patients must take one capsule of <Product name> twice daily.

In patients after a successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD, treatment should not be started until haemostasis is achieved (see section 5.1).

Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

• *ACS, CAD/PAD*

Co-administration with antiplatelet therapy
In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of <Product name> should be evaluated depending on the type of event or procedure and antiplatelet regimen.

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

Converting from Vitamin K Antagonists (VKA) to <Product name>
When converting patients from VKAs to <Product name>, International Normalised Ratio (INR) values could be falsely elevated after the intake of <Product name>. The INR is not valid to measure the anticoagulant activity of <Product name>, and therefore should not be used (see section 4.5).

Converting from <Product name>to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from <Product name> to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that <Product name> can contribute to an elevated INR.
In patients converting from <Product name> to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both <Product name> and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban 2.5 mg/acetylsalicylic acid. Once <Product name> is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

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

Converting from <Product name> to parenteral anticoagulants
Give the first dose of parenteral anticoagulant at the time the next <Product name> dose would be taken.

Special populations

Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. The risk of renal impairment and acute renal failure can be further increased by acetylsalicylic acid. The use of <Product name> is contraindicated in patients with severe renal impairment (see sections 4.3 and 4.4).

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2).

Hepatic impairment
<Product name> is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. Close medical monitoring is required when patients with hepatic impairment are treated with <Product name> (see sections 4.3 and 5.2).

Elderly population
No dose adjustment is necessary (see sections 4.4 and 5.2).
The risk of bleeding increases with increasing age (see section 4.4).

Body weight
No dose adjustment is necessary (see sections 4.4 and 5.2).

Gender
No dose adjustment is necessary (see section 5.2).

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

Method of administration

<Product name> is for oral use.
The capsules can be taken with or without food (see sections 4.5 and 5.2).

For patients who are unable to swallow whole capsules, the capsules may be opened, and the content of the capsule may be crushed and mixed with water immediately prior to use and administered orally.

4.3 Contraindications

Hypersensitivity to the active substances, to other salicylates, or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

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

Haemorrhagic diathesis.

Asthma attacks caused by the administration of salicylates or substances with a similar effect, especially nonsteroidal anti-inflammatory drugs.

Severe renal impairment (creatinine clearance < 30 ml/min).

Severe, uncontrolled cardiac insufficiency.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of

switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).

Concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month (see section 4.4).
Concomitant treatment with methotrexate at a dose of 15 mg or more per week (see section 4.5).
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

In ACS patients, efficacy and safety of rivaroxaban have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine.
In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of rivaroxaban have been investigated in combination with ASA.
In patients after recent revascularisation procedure of the lower limb due to symptomatic PAD, efficacy and safety of rivaroxaban have been investigated in combination with the antiplatelet agent ASA alone or ASA plus short-term clopidogrel. If required, dual antiplatelet therapy with clopidogrel should be short-term; long-term dual antiplatelet therapy should be avoided (see section 5.1).

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

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

Close medical monitoring is required in the following cases in particular:
- Hypersensitivity to other analgesics/anti-inflammatory drugs/antirheumatic drugs or other allergenic substances (see section 4.3)
- Other allergies (e.g. skin reactions, itching, hives)
- Bronchial asthma, hay fever, swelling of the nasal mucosa (nasal polyps) or chronic respiratory disorders
- A history of gastrointestinal ulcers or bleeding
- Patients with hepatic impairment
- Patients with renal impairment or reduced cardiovascular circulation (e.g. renal vascular disease, congestive heart failure, volume loss, major surgery, sepsis, or severe bleeding events): the risk of renal impairment and acute renal failure can be further increased by acetylsalicylic acid
- Prior to surgery (even minor procedures, such as tooth extractions): the tendency to bleed may be increased
- Patients with severe glucose-6-phosphate dehydrogenase deficiency: acetylsalicylic acid can induce haemolysis or haemolytic anaemia. The risk of haemolysis may be increased by factors such as high doses, fever, or acute infections.

At low doses, acetylsalicylic acid reduces uric acid excretion. This can trigger an attack of gout in patients who are at risk, accordingly.

<u>Haemorrhagic risk</u>
As with other anticoagulants, patients taking <Product name> are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. <Product name> administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies, mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. Therefore, the use of <Product name> in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition, these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment
In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. The risk of severe renal impairment can be further increased by acetylsalicylic acid. The use of <Product name> is contraindicated in patients with severe renal impairment (see sections 4.2 and 4.3).

In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations <Product name> is to be used with caution (see section 4.5).

Interaction with other medicinal products
The use of <Product name> is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see sections 4.5 and 5.1).
Patients treated with <Product name> should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk and should be advised to talk to their doctor if they are taking <Product name> and are planning to take NSAIDs, such as ibuprofen and naproxen.

Close medical monitoring is required with concomitant anticoagulant treatment.

Other haemorrhagic risk factors
As with other antithrombotics, <Product name> is not recommended in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy

• bronchiectasis or history of pulmonary bleeding

It should be used with caution in ACS and CAD/PAD patients:
• ≥ 75 years of age if co-administered clopidogrel or ticlopidine. The benefit-risk of the treatment should be individually assessed on a regular basis.
• with lower body weight (< 60 kg) if co-administered with clopidogrel or ticlopidine.
• CAD patients with severe symptomatic heart failure. Study data indicate that such patients may benefit less from treatment with rivaroxaban (see section 5.1).

Patients with cancer
Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.
In patients with malignant neoplasms at high risk of bleeding, the use of <Product name> is contraindicated (see section 4.3).

Patients with prosthetic valves
<Product name> should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of <Product name> have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that <Product name> provides adequate anticoagulation in this patient population. Treatment with <Product name> is not recommended for these patients.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including rivaroxaban, are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. For patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Patients with prior stroke and/or TIA
Patients with ACS
<Product name> is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (see section 4.3). Few ACS patients with a prior stroke or TIA have been studied but the limited efficacy data available indicate that these patients do not benefit from treatment with rivaroxaban.

Patients with CAD/PAD
CAD/PAD patients with previous haemorrhagic or lacunar stroke, or an ischaemic, non-lacunar stroke within the previous month have not been studied (see section 4.3).
Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD with a previous stroke or TIA have not been studied. Treatment with <Product name> should be avoided in these patients receiving dual antiplatelet therapy.

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

anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of <Product name> in these situations.
<Product name> may require discontinuation because platelet aggregation inhibitors typically increase the bleeding risk, and the bleeding time may be prolonged.
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 (see section 5.2). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, <Product name> should be stopped at least 12 hours before the intervention, if possible and based on the clinical judgement of the physician. If a patient is to undergo elective surgery and anti-platelet effect is not desired, <Product name> should be discontinued as platelet aggregation inhibitors might cause prolongation of the bleeding time and an increased bleeding tendency.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
<Product name> should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established as determined by the treating physician (see section 5.2).

Elderly population
Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including acetylsalicylic acid, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly (see sections 5.1 and 5.2).

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). 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. <Product name> 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.

Information about excipients
<Product name> contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed using <Product name>. As <Product name> contains rivaroxaban and acetylsalicylic acid, any interactions that have been identified with these agents individually may occur with <Product name>.

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of <Product name> is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole,

voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in Cmax. The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.
In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1.8 fold increase in mean rivaroxaban AUC and 1.6 fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6 fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with <Product name> should be avoided.

Anticoagulants/Thrombolytic agents
<Product name> can increase the risk of bleeding if taken prior to thrombolytic therapy. Attention must therefore be paid to signs of external or internal bleeding (e.g. bruising) in patients who are to receive thrombolytic therapy.
After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/Anti-inflammatory and antirheumatic drugs
Care is to be taken if patients are treated concomitantly with NSAIDs and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk, and the bleeding time may be prolonged (see section 4.4).
Anti-inflammatory and antirheumatic drugs containing salicylates increase the risk of gastrointestinal ulcers and bleeding.
Concomitant use (on the same day) of some NSAIDs, such as ibuprofen and naproxen, can weaken the irreversible antiplatelet effect of acetylsalicylic acid. The clinical relevance of this interaction is not known. Administration of some NSAIDs such as ibuprofen or naproxen to patients with increased cardiovascular risk may limit the cardioprotective effect of acetylsalicylic acid (see section 4.4).
Experimental data suggest that ibuprofen can inhibit the effect of low-dose acetylsalicylic acid on platelet aggregation when administered concurrently. In a study in which a single dose of 400 mg of ibuprofen was taken 8 hours before or 30 minutes after administration of a fast-release acetylsalicylic acid product (81 mg), the effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation was reduced. However, due to the limited data available and the uncertainties when extrapolating ex vivo data to the clinical situation, it is not possible to draw firm conclusions concerning the regular use of ibuprofen. The occasional use of ibuprofen is unlikely to cause a relevant clinical interaction.

Platelet aggregation inhibitors
Clinically relevant prolongation of bleeding time has been observed after concomitant administration of acetylsalicylic acid platelet aggregation inhibitors, e.g. ticlopidine, clopidogrel.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Systemic glucocorticoids
Systemic glucocorticoids (with the exception of hydrocortisone as a replacement therapy for Addison's disease) increased the risk of gastrointestinal bleeding and ulcers, when co-administered with acetylsalicylic acid.

Alcohol
Alcohol increased the risk of gastrointestinal ulcers and bleeding when co-administered with acetylsalicylic acid.

Digoxin and lithium
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Antidiabetic drugs e.g. sulphonylureas and insulin
Salicylates may increase the hypoglycaemic effect of antidiabetics. Thus, some downward readjustment of the dosage of the antidiabetic may be appropriate if large doses of salicylates are used. Increased blood glucose controls are recommended.

Methotrexate
Acetylsalicylic acid enhances the haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with acetylsalicylic acid is contraindicated. At doses <15 mg/week, weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly (see section 4.3).

Ciclosporin, tacrolimus
Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Valproic acid
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Phenytoin
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.

Carbonic anhydrase inhibitors (acetazolamide)
May result in severe acidosis and increased central nervous system toxicity.

SSRIs/SNRIs

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.

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers
Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.
No clinically relevant interaction with food was observed (see section 4.2).

A weakening of the effect was observed when acetylsalicylic acid was co-administered with aldosterone antagonists (spironolactone and canrenoate), loop diuretics (e.g. furosemide), antihypertensive agents (especially ACE inhibitors), uricosuric agents (e.g. probenecid, benzbromarone).
If used concomitantly, metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation. Metamizole should therefore be used with caution in patients taking <Product name> for cardioprotection.

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety and efficacy of <Product name> have not been established in pregnant women.

Studies with rivaroxaban in animals have shown reproductive toxicity (see section 5.3).

Inhibition of prostaglandin synthesis can have a detrimental effect on pregnancy and/or embryonic/foetal development.
Data from epidemiological studies indicate an increased risk of miscarriage, heart deformities and gastroschisis following the use of a prostaglandin synthesis inhibitor during early pregnancy.

Due to the potential reproductive toxicity, the intrinsic risk of bleeding, the evidence that rivaroxaban passes the placenta, the increased risk of miscarriage, heart deformities and gastroschisis, <Product name> is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with <Product name>.

Breastfeeding
Safety and efficacy of <Product name> have not been established in breast-feeding women.

Data from animals indicate that rivaroxaban is secreted into milk.

Small quantities of the active substance acetylsalicylic acid and its metabolites are excreted in human milk.

Therefore, <Product name> is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
No specific studies with <Product name> in humans have been conducted to evaluate effects on fertility.

In a study on male and female fertility in rats, no effects were seen with administration of rivaroxaban (see section 5.3).

Acetylsalicylic acid belongs to a group of medicines (NSAIDs) which may impair the fertility in women. This effect is reversible on stopping the medicine.

4.7 Effects on ability to drive and use machines

<Product name> has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported during treatment with rivaroxaban (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

No therapeutic clinical trials have been conducted with <Product name> 2.5 mg/ 50 mg hard capsules, however bioequivalence of <Product name> 2.5 mg/50 mg hard capsules with co-administered rivaroxaban and acetylsalicylic acid has been demonstrated through a PK/PD clinical trial (clinical trial PAO-P8-022) (see section 5.1 and 5.2).

Summary of the safety profile
The adverse reactions reported for <Product name> 2.5 mg/50 mg hard capsules during clinical trial PAO-P8-022, were consistent with the known safety profiles of rivaroxaban and acetylsalicylic acid when given as separate medicinal products.
In this trial, 67 healthy subjects received <Product name> 2.5 mg/50 mg hard capsules, and the most commonly reported adverse reactions were headache (7.3%) and constipation (4.4%).

Rivaroxaban

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies. Overall, 69,608 adult patients in nineteen phase III studies and 488 paediatric patients in two phase II and two phase III studies were exposed to rivaroxaban.

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see

section 4.4. and 'Description of selected adverse reactions' below). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Tabulated list of adverse reactions

The adverse reactions reported with rivaroxaban and acetylsalicylic acid treatment, either as monotherapy or in combination, are summarised in Table 1 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
very common (≥ 1/10)
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1,000 to < 1/100)
rare (≥ 1/10,000 to < 1/1,000)
very rare (< 1/10,000)
not known (cannot be estimated from the available data)

Common	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)[a]	Thrombocytosis (incl. platelet count increased)[a,b], thrombocytopenia[a]	Haemorrhage (incl. nose bleeds, bleeding gums, skin bleeding or genitourinary tract bleeding with possibly prolonged bleeding time)[c]		Haemolysis[c], Haemolytic anaemia[c]
Immune system disorders				
	Allergic reaction[a], dermatitis allergic[a], angioedema and allergic oedema[a]	Hypersensitivity (incl. hypersensitivity reactions of the skin, respiratory tract, gastrointestinal tract and cardiovascular system, especially in asthmatics)[c]	Anaphylactic reactions including anaphylactic shock[a]	
Nervous system disorders				
Dizziness[a], headache[a]	Cerebral and intracranial haemorrhage[a,c], syncope[a]			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)[a]				
Cardiac disorders				
	Tachycardia[a]			
Vascular disorders				
Hypotension[a], haematoma[a]				
Respiratory, thoracic and mediastinal disorders				
Epistaxis[a], haemoptysis[a]			Eosinophilic pneumonia[a]	

Gastrointestinal disorders				
Gingival bleeding[a], gastrointestinal tract haemorrhage (incl. rectal haemorrhage)[a,c], gastrointestinal and abdominal pain[a,c], dyspepsia[a,c], nausea[a.c], constipation[a,b], diarrhoea[a,c], vomiting[a,b,c], heartburn[c]	Dry mouth[a], gastrointestinal ulcer[c] gastrointestinal haemorrhage[c], iron deficiency anaemia[c], gastrointestinal inflammation[c]			
Hepatobiliary disorders				
Increase in transaminases[a]	Hepatic impairment[a], increased bilirubin[a], increased blood alkaline phosphatase[a,b], increased GGT[a,b]	Jaundice[a], bilirubin conjugated increased (with or without concomitant increase of ALT)[a], cholestasis[a], hepatitis (incl. hepatocellular injury)[a]		
Common	**Uncommon**	**Rare**	**Very rare**	**Not known**
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalized pruritus)[a], rash[a], ecchymosis[a], cutaneous and subcutaneous haemorrhage[a]	Urticaria[a], skin reaction (incl. very rare cases of erythema multiforme)[c]		Stevens-Johnson syndrome/Toxic Epidermal Necrolysis[a], DRESS syndrome[a]	
Musculoskeletal and connective tissue disorders				
Pain in extremity[a,b]	Haemarthrosis[a]	Muscle haemorrhage[a]		Compartment syndrome secondary to a bleeding[a]
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[d])[a], renal impairment (incl. blood creatinine increased, blood urea increased)[a]			Acute renal failure[c], Renal impairment[c]	Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion[a], Anticoagulant-related nephropathy[a]
General disorders and administration site conditions				

Fever[a,b], peripheral oedema[a], decreased general strength and energy (incl. fatigue and asthenia)[a]	Feeling unwell (incl. malaise)[a]	Localised oedema[a,b]		
Investigations				
	Increased LDH[a,b], increased lipase[a,b], increased amylase[a,b]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage)[a], Contusion[a], wound secretion[a,b]		Vascular pseudoaneurysm[a,e]		
Metabolism and nutrition disorders				
			Hypoglycaemia[c], fractional uric acid excretion[c], gout[c]	

[a]: observed with rivaroxaban when co-administered with acetylsalicylic acid
[b]: observed with rivaroxaban when co-administered with acetylsalicylic acid in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
[c]: observed with acetylsalicylic acid as monotherapy
[d]: observed with rivaroxaban when co-administered with acetylsalicylic acid in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
[e]: observed as uncommon with rivaroxaban when co-administered with acetylsalicylic acid in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

Table 1: Tabulated summary of adverse reactions rivaroxaban and acetylsalicylic acid treatment, either as monotherapy or in combination

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). In clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleeding may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained

shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

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

There have been rare to very rare reports of severe bleeding associated with the use of acetylsalicylic acid, such as cerebral haemorrhage, especially in patients with uncontrolled hypertension and/or on concomitant anticoagulant treatment, which in isolated cases may be life-threatening.
Haemolysis and haemolytic anaemia have been reported in patients with severe glucose-6-phosphate dehydrogenase deficiency, during treatment with acetylsalicylic acid.

Bleeding, such as nose bleeds, bleeding gums, skin bleeding or genitourinary tract bleeding with possibly prolonged bleeding time (see section 4.4). This effect can persist for 4 to 8 days after acetylsalicylic acid administration.

In the event of previous damage to the intestinal mucosa, multiple membranes may develop in the intestinal lumen, potentially followed by stenosis after the administration of acetylsalicylic acid. If black stools or bloody vomiting (signs of severe gastric bleeding) develop, a doctor must be notified immediately.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Rivaroxaban

Rare cases of rivaroxaban overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions (see section “Management of bleeding”).
A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa).
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicinal

products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

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

Acetylsalicylic acid

A distinction is made between chronic overdose from acetylsalicylic acid with predominantly central-nervous disorders such as drowsiness, dizziness, confusion or nausea ("salicylism") and acute intoxication.
A severe acid-base imbalance is the predominant feature of acute acetylsalicylic acid intoxication. Even within the therapeutic dose range, respiratory alkalosis occurs due to an increased respiration rate. This is compensated by the increased renal excretion of hydrogen carbonate, so that the pH of the blood is normal. At toxic doses, such compensation is no longer sufficient and the pH and hydrogen carbonate concentrations in the blood drop. The plasma PCO_2 concentration may at times be normal. The picture would appear to be metabolic acidosis. However, it will actually be a combination of respiratory and metabolic acidosis. The reasons for this are: restricted breathing from toxic doses, accumulation of acid, partly as a result of decreased renal excretion (sulfuric and phosphoric acid as well as salicylic acid, lactic acid, acetoacetic acid, among others) due to impaired carbohydrate metabolism. An electrolyte imbalance thus results. Larger amounts of potassium are lost.

Symptoms of acute intoxication
Symptoms from milder levels of acute intoxication (200 – 400 µg/ml): In addition to disorders of the acid-base balance and electrolyte balance (e.g. potassium loss), hypoglycaemia, skin eruptions and gastrointestinal bleeding, there have been reports of hyperventilation, ringing in the ears, nausea, vomiting, impaired vision and hearing, headache, dizziness and confusion.
In the event of severe intoxication (over 400 µg/ml), delirium, tremor, dyspnoea, sweating, exsiccosis, hyperthermia and coma can occur.
If intoxication proves fatal, respiratory failure is usually the cause of death.

Treatment for intoxication
The options for treating acetylsalicylic acid intoxication depend on the extent, stage and clinical symptoms of the intoxication. They are consistent with the usual measures for reducing absorption of the active substance and controlling the fluid and electrolyte balance and impaired temperature regulation and respiration. Measures to accelerate clearance and return the acid-base and electrolyte balance to normal are the priority. In addition to the use of sodium hydrogen carbonate and potassium chloride infusion solutions, diuretics are also administered. The urine should have a basic reaction so that the ionisation level of the salicylates increases and the rediffusion rate in the tubules thus decreases. Control of the blood concentrations (pH, PCO_2, hydrogen carbonate, potassium, etc.) is highly recommended. Haemodialysis may be necessary in severe cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, platelet aggregation inhibitors excl. heparin, ATC code: B01AF51.

<Product name> 2.5 mg/50 mg hard capsules combine two antithrombotic agents to prevent atherothrombotic events.

Mechanism of action

Rivaroxaban

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

Acetylsalicylic acid

Acetylsalicylic acid has an irreversible antiplatelet effect. This effect is achieved by acetylation of cyclooxygenase. The formation of thromboxane A_2 (a prostaglandin that promotes platelet aggregation and has vasoconstrictive effects) in the platelets is thus irreversibly inhibited. This is a permanent effect which usually lasts for the entire 8-day life span of a platelet.
Paradoxically, acetylsalicylic acid also inhibits the formation of prostacyclin (a prostaglandin with antiplatelet yet vasodilatory effects) in the endothelial cells of the vascular walls. This effect is temporary.
Once the acetylsalicylic acid has been washed out of the blood, prostacyclin is again produced by the nucleated endothelial cells.
Consequently, at low once-daily doses (<100 mg/day), acetylsalicylic acid blocks thromboxane A_2 in the platelets without markedly impairing the production of prostacyclin.

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 is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

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

The activated partial thomboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative anti-factor-Xa tests (see section 5.2).

Clinical efficacy and safety

No therapeutic clinical trials were conducted with <Product name> 2.5 mg/50 mg hard capsules, however, bioequivalence of <Product name> 2.5 mg/50 mg hard capsules with co-administered rivaroxaban and acetylsalicylic acid has been demonstrated (clinical trial PAO-P8-022) (for PK parameters see section 5.2). The demonstration of the pharmacodynamic effect of <Product name> 2.5 mg/50 mg hard capsules was based on a surrogate marker, namely inhibition of thromboxane B_2 (TxB_2)

synthesis, which is considered as a widely accepted surrogate for platelet aggregation and also for efficacy in secondary prevention of cardiovascular events.

PD equivalence of <Product name> 2.5 mg/50 mg hard capsules with co-administered rivaroxaban and acetylsalicylic acid tablets (clinical trial PAO-P8-022)

The primary pharmacodynamic (PD) objective of this study was to demonstrate equivalence following multiple oral dose administrations between <Product name> 2.5 mg/50 mg hard capsules and the individual tablet of Acetylsalicylic acid concomitantly administered with Rivaroxaban, based on the surrogate marker thromboxane B_2 (TxB_2) levels. In this trial, 41 healthy subjects were treated with the test product (1 x <Product name> 2.5 mg/50 mg hard capsules) administered twice daily (approximately 12 hours apart) for 8 consecutive days (for a total of 16 administrations). 42 healthy subjects (including 10 obese) were treated with the Reference-1 product (1 × 2.5 mg Rivaroxaban (Xarelto®) film-coated tablet) administered BID for 8 consecutive days, in the mornings and evenings (approximately 12 hours apart), for a total of 16 administrations and Reference-2 (1 × 100 mg Acetylsalicylic acid (Aspirin®) tablet) administered once a day (QD) in the morning for 8 consecutive days, for a total of 8 administrations. For the morning drug administrations, Reference-1 and Reference-2 were administered concomitantly.

The following PD parameters were estimated following 8 consecutive administration days, to demonstrate therapeutic equivalence:

- TxB_2 concentration after 24 hours (C_{24}) (Table 2)
- TxB_2 area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) (Table 2)
- Subjects' responsiveness to treatment (Test or Reference) (Table 3)

Parameter	**Geometric LSmeans[a]**		**95% Confidence Intervals (%)**		
	Treatment-3 (Test) **N=38**	**Treatment-4** (Reference) **N=40**	**Ratio (%)**	**Lower**	**Upper**
C_{24}	2.41	4.45	54.19	49.07	59.86
AUC_{0-24}	25.54	41.48	61.56	55.00	68.91

[a] units are ng/mL for C_{24} and ng·h/mL for AUC_{24}

Table 2. Comparison of statistical results for TxB_2 following 8 consecutive administration days (PAO P8-022)

The equivalence limit estimation was based on the target therapeutic range of surrogate marker TxB_2 (1 ng/mL to 10 ng/mL), which corresponds to inhibition of TxB_2 > 97%. Following 8 consecutive administration days, the upper bound limit of the 95% confidence interval (CI) calculated from the exponential of the ln-transformed parameters C_{24} in the Test group and in the Reference group, were within the therapeutic target (<10 ng/mL) with values of 2.59 ng/mL and 4.77 ng/mL respectively (see Table 2).

Following 8 consecutive administration days, the Test/Reference ratios (95% CI) are 54.19% (49.07-59.86%) for C_{24} and 61.56% (55.00-68.91%) for AUC_{24}. The statistical results indicate that the Test /Reference ratios of geometric LSmeans, and the 95% CI of C_{24} and AUC_{0-24} were within the equivalence margins (see Table 2). Based on comparable results of the surrogate marker TxB_2 levels, test product is judged to be therapeutically equivalent to reference product administered under fasting conditions to healthy adult subjects and in subjects with obesity.

Subjects' responsiveness to treatment (test or reference) was also evaluated and categorized. Subjects were categorized as responder (inhibition as successful treatment: I_{24} >97%, responder with incomplete inhibition: I_{24} ≥95% and ≤97%), or non-responder (inhibition as treatment failure: I_{24} <95%) (Table 3).

Table 3 presents the summary of subject's responsiveness to ASA after 8-day oral dose administration of the FDC product (Test – administered BID) and the co-administration of Xarelto® (BID) and Aspirin® (100 mg QD) based inhibition categories of the surrogate marker TxB_2.

	Treatment			
	Treatment-3 (Test) **N=42**		**Treatment-4** (Reference) **N=42**	
Responsiveness	**n**	**(%)**	**n**	**(%)**
Responder (I_{24} > 97%)	40	100.00	41	97.62
Incomplete Responder (I_{24} ≥ 95% and ≤ 9	0	0.00	1	2.38
Non-Responder (I_{24} < 95%)	0	0.00	0	0.00

Table 3. Summary of Subjects Responsiveness on Day 8 Following Multiple Dose Administration – Pharmacodynamic Population (PAO P8-022)

After 8 days of treatment administration, all subjects (100%) responded to the Test product (I_{24}>97%) and 41 out of 42 subjects (97.62%) responded to the Reference product (I_{24}>97%), suggesting equivalent degree of inhibition between Test and Reference formulations (see Table 3).

<Product Name> was shown to provide similar therapeutic effect with regards to prevention of atherothombotic events (via the surrogate marker TxB_2), when compared with the standard treatment, i.e. co-administration of rivaroxaban and ASA, despite the difference on the dosing of the ASA component (BID vs QD).

Rivaroxaban

ACS

The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of cardiovascular (CV) death, myocardial infarction (MI) or stroke in subjects with a recent ACS (ST-elevation myocardial infarction [STEMI], non- ST-elevation myocardial infarction [NSTEMI] or unstable angina [UA]). In the pivotal double-blind ATLAS ACS 2 TIMI 51 study, 15,526 patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups: rivaroxaban 2.5 mg orally twice daily, 5 mg orally twice daily or to placebo twice daily co-administered with ASA alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine). Patients with an ACS under the age of 55 had to have either diabetes mellitus or a previous MI. The median time on treatment was 13 months and overall treatment duration was up to almost 3 years. 93.2% of patients received ASA concomitantly plus thienopyridine treatment and 6.8% ASA only. Among patients receiving dual anti-platelets therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3% received prasugrel. Patients received the first dose of rivaroxaban at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.

Both the 2.5 mg twice daily and the 5 mg twice daily regimens of rivaroxaban were effective in further reducing the incidence of CV events on a background of standard antiplatelet care. The 2.5 mg twice daily regimen reduced mortality, and there is evidence that the lower dose had lower bleeding risks, therefore rivaroxaban 2.5 mg twice daily co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine is recommended for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers.

Relative to placebo, rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 5 and Figure 1). Also, the first secondary endpoint (all-cause death, MI or stroke) was reduced significantly. An additional retrospective analysis showed a nominally significant reduction in the incidence rates of stent thrombosis compared with placebo (see Table 4). The incidence rates for the principal safety outcome (non-coronary artery bypass graft (CABG) TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo (see Table 6). However, the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding.

In Table5 the efficacy results of patients undergoing percutaneous coronary intervention (PCI) are presented. The safety results in this subgroup of patients undergoing PCI were comparable to the overall safety results.

Patients with elevated biomarkers (troponin or CK-MB) and without a prior stroke/TIA constituted 80% of the study population. The results of this patient population were also consistent with the overall efficacy and safety results.

Study population	**Patients with a recent acute coronary syndrome** [a)]	
Treatment dose	**Rivaroxaban 2.5 mg, twice daily, N=5,114 n (%) Hazard Ratio (HR) (95% CI) p-value** [b)]	**Placebo N=5,113 n (%)**
Cardiovascular death, MI or stroke	313 (6.1%) 0.84 (0.72, 0.97) p = 0.020*	376 (7.4%)
All-cause death, MI or stroke	320 (6.3%) 0.83 (0.72, 0.97) p = 0.016*	386 (7.5%)
Cardiovascular death	94 (1.8%) 0.66 (0.51, 0.86) p = 0.002**	143 (2.8%)
All-cause death	103 (2.0%) 0.68 (0.53, 0.87) p = 0.002**	153 (3.0%)
MI	205 (4.0%) 0.90 (0.75, 1.09) p = 0.270	229 (4.5%)
Stroke	46 (0.9%) 1.13 (0.74, 1.73) p = 0.562	41 (0.8%)
Stent thrombosis	61 (1.2%) 0.70 (0.51, 0.97) p = 0.033**	87 (1.7%)

[a)] modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
[b)] vs placebo; Log-Rank p-value
* statistically superior
** nominally significant

Table 4. Efficacy results from phase III ATLAS ACS 2 TIMI 51

Study population	**Patients with recent acute coronary syndrome undergoing PCI** [a)]	
Treatment dose	**Rivaroxaban 2.5 mg, twice daily, N=3114 n (%) HR (95% CI) p-value** [b)]	**Placebo N=3096 n (%)**
Cardiovascular death, MI or stroke	153 (4.9%) 0.94 (0.75, 1.17) p = 0.572	165 (5.3%)

Cardiovascular death	24 (0.8%) 0.54 (0.33, 0.89) p = 0.013**	45 (1.5%)
All-cause death	31 (1.0%) 0.64 (0.41, 1.01) p = 0.053	49 (1.6%)
MI	115 (3.7%) 1.03 (0.79, 1.33) p = 0.829	113 (3.6%)
Stroke	27 (0.9%) 1.30 (0.74, 2.31) p = 0.360	21 (0.7%)
Stent thrombosis	47 (1.5%) 0.66 (0.46, 0.95) p = 0.026**	71 (2.3%)

[a)] modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
[b)] vs placebo; Log-Rank p-value
** nominally significant

Table 5. Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI

Study population	**Patients with recent acute coronary syndrome [a)]**	
Treatment dose	**Rivaroxaban 2.5 mg, twice daily, N=5,115 n (%) HR (95% CI) p-value [b)]**	**Placebo N=5,125 n(%)**
Non-CABG TIMI major bleeding event	65 (1.3%) 3.46 (2.08, 5.77) p = < 0.001*	19 (0.4%)
Fatal bleeding event	6 (0.1%) 0.67 (0.24, 1.89) p = 0.450	9 (0.2%)
Symptomatic intracranial haemorrhage	14 (0.3%) 2.83 (1.02, 7.86) p = 0.037	5 (0.1%)
Hypotension requiring treatment with intravenous inotropic agents	3 (0.1%)	3 (0.1%)
Surgical intervention for ongoing bleeding	7 (0.1%)	9 (0.2%)
Transfusion of 4 or more units of blood over a 48 hour period	19 (0.4%)	6 (0.1%)

[a)] safety population, on treatment
[b)] vs placebo; Log-Rank p-value
* statistically significant

Table 6. Safety results from phase III ATLAS ACS 2 TIMI 51

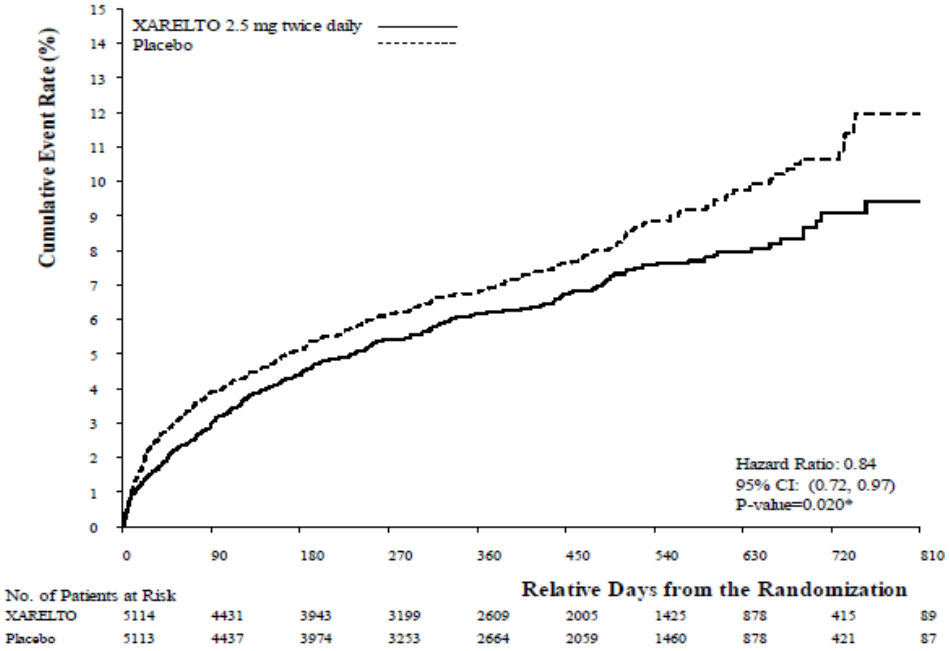


Figure 1. Time to first occurrence of primary efficacy endpoint (CV death, MI or stroke)

CAD/PAD

The phase III 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 or symptomatic PAD at high risk of ischaemic events. Patients were followed for a median of 23 months and maximum of 3.9 years.

Subjects without a continuous need for treatment with a proton pump inhibitor were randomised to pantoprazole or placebo. All patients were then randomised 1:1:1 to rivaroxaban 2.5 mg twice daily/ASA 100 mg once daily, to rivaroxaban 5 mg twice daily, or ASA 100 mg once daily alone, and their matching placebos.

CAD patients had multivessel CAD and/or prior MI. For patients < 65 years of age atherosclerosis involving at least two vascular beds or at least two additional cardiovascular risk factors were required.

PAD patients had previous interventions such as bypass surgery or percutaneous transluminal angioplasty or limb or foot amputation for arterial vascular disease or intermittent claudication with ankle/arm blood pressure ratio < 0.90 and/ or significant peripheral artery stenosis or previous carotid revascularisation or asymptomatic carotid artery stenosis ≥ 50%.

Exclusion criteria included the need for dual antiplatelet or other non-ASA antiplatelet or oral anticoagulant therapy and patients with high bleeding risk, or heart failure with ejection fraction < 30% or New York Heart Association class III or IV, or any ischaemic, non-lacunar stroke within 1 month or any history of haemorrhagic or lacunar stroke.

Rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily was superior to ASA 100 mg, in the reduction of the primary composite outcome of CV death, MI, stroke (see Table 7 and Figure 2).

There was a significant increase of the primary safety outcome (modified ISTH major bleeding events) in patients treated with rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 8).

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 use of pantoprazole 40 mg once daily in addition to antithrombotic study medication in patients with no clinical need for a proton pump inhibitor showed no benefit in the prevention of upper gastrointestinal events (i.e. composite of upper gastrointestinal bleeding, upper gastrointestinal ulceration, or upper gastrointestinal obstruction or perforation); the incidence rate of upper gastrointestinal events was 0.39/100 patient-years in the pantoprazole 40 mg once daily group and 0.44/100 patient-years in the placebo once daily group.

Study population	**Patients with CAD/PAD** [a]					
Treatment dose	Rivaroxaban **2.5 mg bid in combination with ASA 100 mg od N=9152**		**ASA 100 mg od N=9126**			
	Patients with events	**KM %**	**Patients with events**	**KM %**	**HR (95% CI)**	**p-value** [b]
Stroke, MI or CV death	379 (4.1%)	5.20%	496 (5.4%)	7.17%	0.76 (0.66;0.86)	p = 0.00004*
- Stroke	83 (0.9%)	1.17%	142 (1.6%)	2.23%	0.58 (0.44;0.76)	p = 0.00006
- MI	178 (1.9%)	2.46%	205 (2.2%)	2.94%	0.86 (0.70;1.05)	p = 0.14458
- CV death	160 (1.7%)	2.19%	203 (2.2%)	2.88%	0.78 (0.64;0.96)	p = 0.02053
All-cause mortality	313 (3.4%)	4.50%	378 (4.1%)	5.57%	0.82 (0.71;0.96)	
Acute limb ischaemia	22 (0.2%)	0.27%	40 (0.4%)	0.60%	0.55 (0.32;0.92)	

[a] intention to treat analysis set, primary analyses
[b] vs ASA 100 mg; Log-Rank p-value
* The reduction in the primary efficacy outcome was statistically superior.
bid: twice daily; CI: confidence interval; KM %: Kaplan-Meier estimates of cumulative incidence risk calculated at 900 days; CV: cardiovascular; MI: myocardial infarction; od: once daily

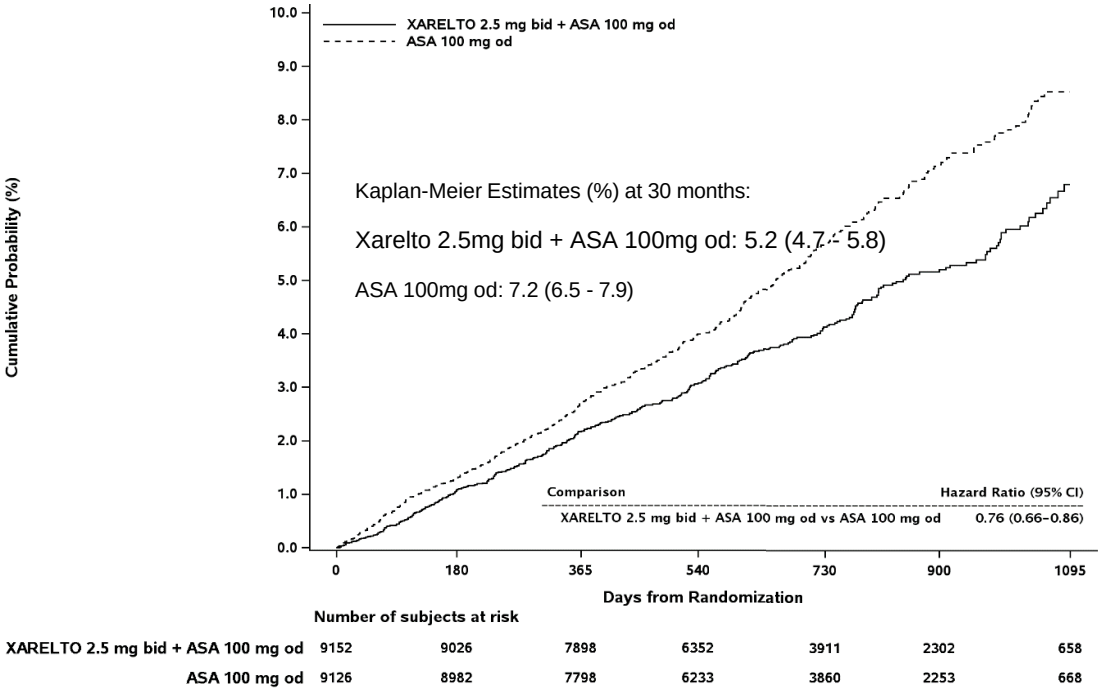
Table 7. Efficacy results from phase III COMPASS

Study population	**Patients with CAD/PAD** [a]		
Treatment dose	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)**	**ASA 100 mg od N=9126 n (Cum.risk %)**	**Hazard Ratio (95 % CI) p-value** [b]
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)] vs ASA 100 mg; Log-Rank p-value
bid: twice daily; CI: confidence interval; Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months; ISTH: International Society on Thrombosis and Haemostasis; od: once daily

Table 8. Safety results from phase III COMPASS



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

Figure 2. Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS

Patients after recent revascularisation procedure of the lower limb due to symptomatic PAD

In the pivotal phase III double-blind **VOYAGER PAD** trial, 6,564 patients after recent successful revascularisation procedure of the lower limb (surgical or endovascular including hybrid procedures) due to symptomatic PAD were randomly assigned to one of two antithrombotic treatment groups: rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily, or to ASA 100 mg once daily, in a 1:1 fashion. Patients were allowed to additionally receive standard dose of clopidogrel once

daily for up to 6 months. The objective of the study was to demonstrate the efficacy and safety of rivaroxaban plus ASA for the prevention of myocardial infarction, ischaemic stroke, CV death, acute limb ischaemia, or major amputation of a vascular etiology in patients after recent successful lower limb revascularisation procedures due to symptomatic PAD. Patients aged ≥ 50 years with documented moderate to severe symptomatic lower extremity atherosclerotic PAD evidenced by all of the following: clinically (i.e. functional limitations), anatomically (i.e. imaging evidence of PAD distal to external iliac artery) and haemodynamically (ankle-brachial-index [ABI] ≤ 0.80 or toe-brachialindex [TBI] ≤ 0.60 for patients without a prior history of limb revascularisation or ABI ≤ 0.85 or TBI ≤ 0.65 for patients with a prior history of limb revascularisation) were included. Patients in need of dual antiplatelet therapy for > 6 months, or any additional antiplatelet therapy other than ASA and clopidogrel, or oral anticoagulant therapy, as well as patients with a history of intracranial haemorrhage, stroke, or TIA, or patients with eGFR < 15 mL/min were excluded.

The mean duration of follow-up was 24 months and the maximum follow-up was 4.1 years. The mean age of the enrolled patients was 67 years and 17% of the patient population were > 75 years. The median time from index revascularisation procedure to start of study treatment was 5 days in the overall population (6 days after surgical and 4 days after endovascular revascularisation including hybrid procedures). Overall, 53.0% of patients received short term background clopidogrel therapy with a median duration of 31 days. According to study protocol study treatment could be commenced as soon as possible but no later than 10 days after a successful qualifying revascularisation procedure and once hemostasis had been assured.

Rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily was superior in the reduction of the primary composite outcome of myocardial infarction, ischaemic stroke, CV death, acute limb ischaemia and major amputation of vascular etiology compared to ASA alone (see Table 9). The primary safety outcome of TIMI major bleeding events was increased in patients treated with rivaroxaban and ASA, with no increase in fatal or intracranial bleeding (see Table 10). The secondary efficacy outcomes were tested in a prespecified, hierarchical order (see Table 9).

Study Population	**Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD** [a)]		
Treatment Dosage	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=3,286 n (Cum. risk %)**[c)]	**ASA 100 mg od N=3,278 n (Cum. risk %)**[c)]	**Hazard Ratio (95% CI)** [d)]
Primary efficacy outcome[b)]	**508 (15.5%)**	**584 (17.8%)**	**0.85 (0.76;0.96) p = 0.0043** [e)]*
- MI	131 (4.0%)	148 (4.5%)	0.88 (0.70;1.12)
- Ischaemic stroke	71 (2.2%)	82 (2.5%)	0.87 (0.63;1.19)
- CV death	199 (6.1%)	174 (5.3%)	1.14 (0.93;1.40)
- Acute limb ischaemia [f)]	155 (4.7%)	227 (6.9%)	0.67 (0.55;0.82)
- Major amputation of vascular etiology	103 (3.1%)	115 (3.5%)	0.89 (0.68;1.16)
Secondary efficacy outcome			
Unplanned index limb revascularisation for recurrent limb ischaemia	584 (17.8%)	655 (20.0%)	0.88 (0.79;0.99) p = 0.0140 [e)]*

Hospitalisation for a coronary or peripheral cause (either lower limb) of a thrombotic nature	262 (8.0%)	356 (10.9%)	0.72 (0.62;0.85) p < 0.0001 e)*
All-cause mortality	321 (9.8%)	297 (9.1%)	1.08 (0.92;1.27)
VTE events	25 (0.8%)	41 (1.3%)	0.61 (0.37;1.00)

a) intention to treat analysis set, primary analyses; ICAC adjudicated

b) composite of MI, ischaemic stroke, CV death (CV death and unknown cause of death), ALI, and major amputation of vascular etiology

c) only the first occurrence of the outcome event under analysis within the data scope from a subject is considered

d) HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use with treatment as the only covariate.

e) One sided p-value is based on the log-rank test stratified by type of procedure and clopidogrel use with treatment as factor.

f) acute limb ischaemia is defined as sudden significant worsening of limb perfusion, either with new pulse deficit or requiring therapeutic intervention (i.e. thrombolysis or thrombectomy, or urgent revascularisation), and leading to hospitalisation

* The reduction in the efficacy outcome was statistically superior.

ALI: acute limb ischaemia; bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction; CV: cardiovascular; ICAC: Independent Clinical Adjudication Committee

Table 9. Efficacy results from phase III VOYAGER PAD

Study Population	**Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD** a)		
Treatment Dosage	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=3,256 n (Cum. Risk %)**b)	**ASA 100 mg od N=3,248 n (Cum. Risk %)**b)	**Hazard Ratio (95% CI)** c) **p-value** d)
TIMI major bleeding (CABG / non-CABG)	62 (1.9%)	44 (1.4%)	1.43 (0.97;2.10) p = 0.0695
- Fatal bleeding	6 (0.2%)	6 (0.2%)	1.02 (0.33;3.15)
- Intracranial bleeding	13 (0.4%)	17 (0.5%)	0.78 (0.38;1.61)
- Overt bleeding associated with drop Hb ≥ 5g/dL / Hct ≥ 15%	46 (1.4%)	24 (0.7%)	1.94 (1.18;3.17)
ISTH major bleeding	140 (4.3%)	100 (3.1%)	1.42 (1.10;1.84) p = 0.0068
- Fatal bleeding	6 (0.2%)	8 (0.2%)	0.76 (0.26;2.19)
- Non-fatal critical organ bleeding	29 (0.9%)	26 (0.8%)	1.14 (0.67;1.93)
ISTH clinically relevant non-major bleeding	246 (7.6%)	139 (4.3%)	1.81 (1.47;2.23)

a) Safety analysis set (all 27andomized subjects with at least one dose of study drug), ICAC: Independent Clinical Adjudication Committee

b) n = number of subjects with events, N = number of subjects at risk, % = 100 * n/N, n/100p-yrs = ratio of number of subjects with incident events / cumulative at-risk time

c) HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use with treatment as the only covariate

d) Two sided p-value is based on the log rank-test stratified by type of procedure and clopidogrel use with treatment as a factor

Table 10. Safety results from phase III VOYAGER PAD

<u>CAD with heart failure</u>

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 enrollment. 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 twice daily 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 section CAD/PAD).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with <Product name> in all subsets of the paediatric population in the prevention of atherothrombotic events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

A single and multiple dose crossover study evaluated the pharmacokinetics and pharmacodynamics of <Product name> 2.5 mg/50 mg hard capsules taken twice daily, versus individual tablets of 2.5 mg rivaroxaban taken twice daily and 100 mg acetylsalicylic acid taken once daily in healthy subjects and in subjects with obesity (see section 5.1).

The study demonstrated that the single dose pharmacokinetics of the rivaroxaban component of the <Product name> 2.5 mg/50 mg hard capsules are bioequivalent to rivaroxaban concomitantly administered with acetylsalicylic acid (ASA) as individual medicinal products**.** PD equivalence between <Product name> 2.5 mg/50 mg hard capsules and the individual tablet of Acetylsalicylic acid concomitantly administered with Rivaroxaban is presented in Section 5.1.

The following information reflect the pharmacokinetic properties of the individual active substances of <Product name> 2.5 mg/50 mg hard capsules.

Absorption

Rivaroxaban

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg. Rivaroxaban 2.5 mg and can be taken with or without food.

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Acetylsalicylic acid
Depending on the galenic formulation, acetylsalicylic acid is rapidly and completely absorbed after oral administration. The residual acetyl portion of acetylsalicylic acid undergoes partial hydrolytic cleavage while passing through the mucous membranes of the gastrointestinal tract.
Maximum plasma concentrations are reached after 10–20 min (acetylsalicylic acid) and 0.3–2 h (total salicylate), respectively.

Distribution

Rivaroxaban
Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.

Acetylsalicylic acid
Protein binding in human plasma is concentration-dependent; values of 49% to over 70% (acetylsalicylic acid) and 66% to 98% (salicylic acid) have been found.
Salicylic acid can be detected in the cerebrospinal fluid and synovial fluid after oral administration of acetylsalicylic acid.
Salicylic acid crosses the placenta and passes into the breast milk.

Biotransformation and elimination

Rivaroxaban
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.
Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on in vitro investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Acetylsalicylic acid
Acetylsalicylic acid is converted into its main metabolite, salicylic acid, before, during and after absorption. Metabolites are mainly excreted by the kidneys.
In addition to salicylic acid, the main metabolites of acetylsalicylic acid are the glycine conjugate of salicylic acid (salicyluric acid), the ether and ester glucuronides of salicylic acid (salicyl phenolic glucuronide and salicyl acetyl glucuronide), and gentisic acid produced by oxidation of salicylic acid and its glycine conjugate.

The elimination kinetics of salicylic acid are largely dose-dependent, as the capacity for metabolism of salicylic acid is limited (the elimination half-life fluctuates between 2 and 30 h).
The elimination half-life of acetylsalicylic acid is only a few minutes; the elimination half-life of salicylic acid is 2 h after a dose of 0.5 g acetylsalicylic acid and 4 h after 1 g; it increases to 20 h after a single dose of 5 g.

Special populations

Gender
Studies have showed that there were no clinically relevant differences in rivaroxaban pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population
Elderly patients exhibited higher plasma concentrations of rivaroxaban than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance based on the results of a study that was performed. No dose adjustment is necessary.

Different weight categories
Studies have shown that extremes in body weight (< 50 kg or > 120 kg) have only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment is necessary.

Inter-ethnic differences
Based on the results from studies that have taken place, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients have been observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment
Results from studies have shown that cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment
A study showed that there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more

pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients
In patients with ACS receiving rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events, the geometric mean concentration (90% prediction interval) 2 - 4 h and about 12 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 47 (13 - 123) and 9.2 (4.4 - 18) mcg/l, respectively as shown by a study that took place.

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor-Xa inhibition, PT, aPTT, Heptest) has been evaluated in a study that was performed after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor-Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

Paediatric population
Safety and efficacy of <Product name> 2.5 mg/50 mg hard capsules have not been established in children and adolescents up to 18 years of age.

5.3 Preclinical safety data

Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available.
Studies with rivaroxaban in animals have shown reproductive toxicity. Data from animals indicate that rivaroxaban is secreted into milk. In a study on male and female fertility in rats no effects were seen with administration of rivaroxaban.

The toxicological safety profile of rivaroxaban and acetylsalicylic acid has been established in animal experiments and in humans from extensive clinical experience. There are no new preclinical data of relevance which are additional to the data already presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Lactose
Cellulose, microcrystalline (E460)
Sodium laurilsulfate
Poloxamer
Croscarmellose sodium
Magnesium stearate (E470b)

Capsule shell
Titanium dioxide (E171)

Water, purified
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Aluminium-OPA/Alu/PVC blisters:
18 months

HDPE bottles:
2 years
After first opening of the bottle: 2 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

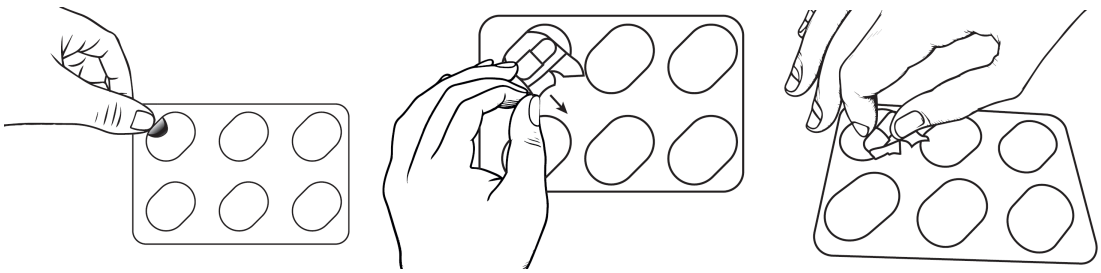
Unit packs containing 56 hard capsules and multipacks of 196 (4 packs of 49) hard capsules in Aluminium-OPA/Alu/PVC blisters.
HDPE bottles with desiccant and with a PP child resistant closure containing 56 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

The capsule should be removed from the blister pocket with caution after tearing the aluminum foil near the edge of the pocket on the bottom side of the blister as depicted on the images below.



7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-11-17