ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg rivaroxaban.

Excipient with known effect

Each film-coated tablet contains 27.90 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light yellow coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with “IL4” on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rivaroxaban Accord, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus 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).

Rivaroxaban Accord, co-administered with acetylsalicylic acid (ASA), 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

The recommended dose is 2.5 mg twice daily.

- *ACS*

Patients taking Rivaroxaban Accord 2.5 mg twice daily should also take a daily dose of 75-100 mg ASA or a daily dose of 75-100 mg ASA 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 rivaroxaban 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 taking Rivaroxaban Accord 2.5 mg twice daily should also take a daily dose of 75-100 mg ASA.

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 Rivaroxaban Accord 2.5 mg twice daily should be evaluated depending on the type of event or procedure and antiplatelet regimen.

Safety and efficacy of rivaroxaban 2.5 mg twice daily in combination with dual antiplatelet therapy have been studied in patients
- with recent ACS in combination with ASA plus clopidogrel/ticlopidine (see section 4.1), and
- after recent revascularisation procedure of the lower limb due to symptomatic PAD in combination with ASA and, if applicable, short-term clopidogrel use (see sections 4.4 and 5.1)

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 rivaroxaban
When converting patients from VKAs to rivaroxaban, International Normalised Ratio (INR) values could be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used (see section 4.5).

Converting from rivaroxaban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.
In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord 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 rivaroxaban
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

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

Special populations

Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Accord is to be

used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
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
Rivaroxaban Accord 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 sections 4.3 and 5.2).

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

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

Gender
No dose adjustment (see section 5.2).

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

Method of administration

Rivaroxaban Accord is for oral use.
The tablets can be taken with or without food (see sections 4.5 and 5.2).

Crushing of tablets
For patients who are unable to swallow whole tablets, Rivaroxaban Accord tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.
The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

4.3 Contraindications

Hypersensitivity to the active substance 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.

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).

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 2.5 mg twice daily 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 2.5 mg twice daily 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 2.5 mg twice daily 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.

Haemorrhagic risk

As with other anticoagulants, patients taking Rivaroxaban Accord are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban Accord 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 rivaroxaban 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.
Rivaroxaban Accord is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).
In patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations rivaroxaban is to be used with caution (see section 4.5).

Interaction with other medicinal products

The use of Rivaroxaban Accord 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), acetylsalicylic acid (ASA) 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 rivaroxaban and antiplatelet agents should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk.

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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 with ASA alone or with ASA plus 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 ASA alone or with ASA plus 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 rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves

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

Patients with prior stroke and/or TIA

Patients with ACS
Rivaroxaban 2.5 mg 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.

Patients with CAD/PAD
CAD/PAD patients with previous haemorrhagic or lacunar stroke, or an ischaemic, non-lacunar stroke with in the previous month were not studied (see section 4.3).
Patients after recent revascularisation procedures of the lower limb due to symptomatic PAD with a previous stroke or TIA were not studied. Treatment with Rivaroxaban 2.5 mg should be avoided in these patients receiving dual antiplatelet therapy.

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. In particular 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.

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 Rivaroxaban 2.5 mg and antiplatelet agents in these situations. Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.
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, Rivaroxaban Accord 2.5 mg 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, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban Accord 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

Increasing age may increase haemorrhagic risk (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. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Rivaroxaban Accord 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 tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

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

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

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).

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 rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of rivaroxaban have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, rivaroxaban is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

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.

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

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1-21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

*Patients exposed to at least one dose of rivaroxaban
** From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8 % of patients	5.9 % of patients
Prevention of venous thromboembolism in medically ill patients	12.6 % of patients	2.1 % of patients
Treatment of DVT, PE and prevention of recurrence	23 % of patients	1.6 % of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years	39.5% of patients	4.6 % of patients

following initiation of standard anticoagulation treatment		
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.
** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied
*** A selective approach to adverse event collection was applied
# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

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

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				

Common	Uncommon	Rare	Very rare	Not known
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		

Common	Uncommon	Rare	Very rare	Not known
Investigations				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

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 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 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 bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see 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.

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

Rare cases of 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”). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR 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 thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Clinical efficacy and safety

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 antiplatelets 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 4 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 Table 5 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.

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

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%)

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 (%)**
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 5: Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI

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

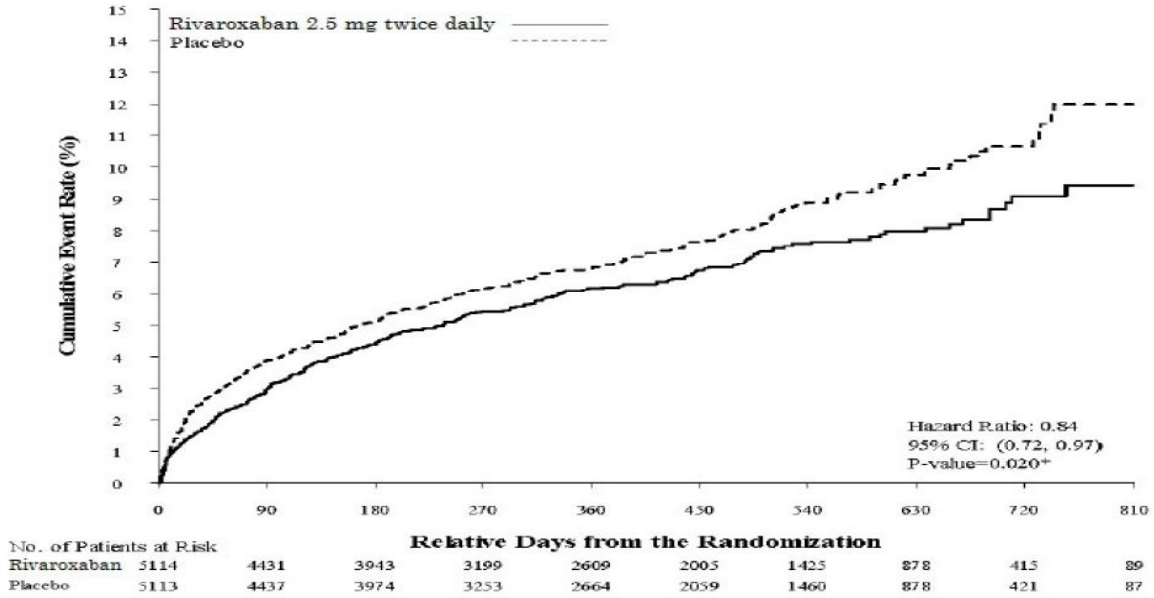
Table 6: Safety results from phase III ATLAS ACS 2 TIMI 51

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

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 revascularization 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.

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**		**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

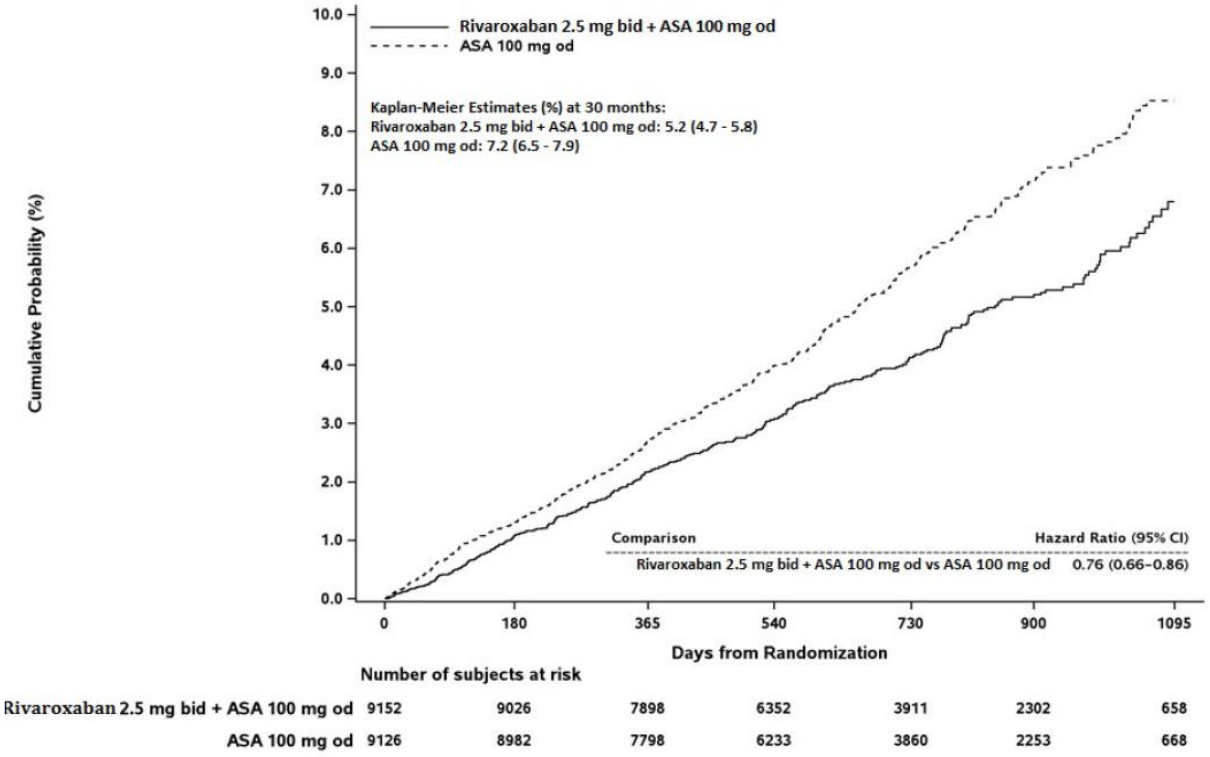
Table 8: Safety results from phase III COMPASS

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

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)**
- 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

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



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

Patients 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-brachial-index [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).

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=3,286 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 10: Safety 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 randomised 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

CAD with heart failure

The **COMMANDER HF** study included 5,022 patients with heart failure and significant coronary artery disease (CAD) following a hospitalization 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).

Patients with high risk triple positive antiphospholipid syndrome

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing rivaroxaban in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100 %) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food.
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

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

Biotransformation and elimination

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

Special populations

Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

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

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

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

Renal impairment
There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 – 49 ml/min) and severe (creatinine clearance 15 – 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6-fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 – 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events in patients with ACS 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.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 – 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 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 have not been established in the indications ACS and CAD/PAD for children and adolescents up to 18 years.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating

Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)

Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC/Aluminium blisters in cartons of 28, 56, 98, 100, 168 or 196 film-coated tablets or perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.
HDPE bottle fitted with white opaque child resistant polypropylene closure and induction sealing liner wad. Pack size 30 or 90 film-coated tablets.
HDPE bottle fitted with white opaque continuous thread polypropylene screw closure and induction sealing liner wad. Pack size 500 film-coated tablets.

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.

Crushing of tablets
Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. Enteral feeding is not required immediately after administration of the 2.5 mg tablets.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/001-011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2020
Date of latest renewal: 6th August 2025

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rivaroxaban.

Excipient with known effect

Each film-coated tablet contains 27.90 mg lactose (as monohydrate), see section 4.4.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Light pink to pink coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with "IL1" on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

4.2 Posology and method of administration

Posology

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take Rivaroxaban Accord immediately and then continue the following day with once daily intake as before.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE. Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Accord 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	Time period	**Dosing schedule**	**Total daily dose**
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Rivaroxaban Accord immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to rivaroxaban
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to rivaroxaban, International Normalised Ratio (INR) values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used (see section 4.5).

Converting from rivaroxaban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.
In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord 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 rivaroxaban
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

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

<u>Special populations</u>

Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Accord is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

- For the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, 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).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50-80 ml/min) (see section 5.2).
  In patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2).
  When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Hepatic impairment
Rivaroxaban Accord 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 sections 4.3 and 5.2).

Elderly population
No dose adjustment (see section 5.2)

Body weight
No dose adjustment (see section 5.2)

Gender
No dose adjustment (see section 5.2)

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

Method of administration

Rivaroxaban Accord is for oral use.
The tablets can be taken with or without food (see sections 4.5 and 5.2).

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

The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

4.3 Contraindications

Hypersensitivity to the active substance 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.

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).

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 breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

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

Haemorrhagic risk

As with other anticoagulants, patients taking Rivaroxaban Accord are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban Accord 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 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.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving rivaroxaban for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (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. Rivaroxaban Accord is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).
In patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations Rivaroxaban Accord is to be used with caution (see section 4.5).

Interaction with other medicinal products

The use of Rivaroxaban Accord 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), acetylsalicylic acid (ASA) 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 section 4.5).

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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

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 rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Accord 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. In particular 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.

Hip fracture surgery

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

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.
The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2).
At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

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

If an invasive procedure or surgical intervention is required, Rivaroxaban Accord 10 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban Accord 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

Increasing age may increase haemorrhagic risk (see section 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. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Rivaroxaban Accord 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 tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

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

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

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

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

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).

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 rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of rivaroxaban have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, rivaroxaban is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

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.

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

Indication	**Number of patients***	**Total daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an acute coronary syndrome (ACS)	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA	31 months

		plus clopidogrel or ticlopidine	
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

*Patients exposed to at least one dose of rivaroxaban
** From the VOYAGER PAD study
The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.
** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied
*** A selective approach to adverse event collection was applied
# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

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

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of	Urticaria		Stevens-Johnson syndrome/ Toxic	

Common	Uncommon	Rare	Very rare	Not known
generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage			Epidermal Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		
Investigations				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

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 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 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 bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see 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.

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

Rare cases of 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"). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 – 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15 s).
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Clinical efficacy and safety

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of VTE, i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme.
Rivaroxaban 10 mg once daily (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.
In all three phase III studies (see table 4), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE and death) and major VTE (proximal DVT, non-fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, nonfatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin. The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

Table 4: Efficacy and safety results from phase III clinical studies

	RECORD 1			RECORD 2			RECORD 3		
Study population	**4,541 patients undergoing total hip replacement surgery**			**2,509 patients undergoing total hip replacement surgery**			**2,531 patients undergoing total knee replacement surgery**		
Treatment dose and duration after surgery	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
Total VTE	18 (1.1 %)	58 (3.7 %)	< 0.001	17 (2.0 %)	81 (9.3 %)	< 0.001	79 (9.6 %)	166 (18.9 %)	< 0.001
Major VTE	4 (0.2 %)	33 (2.0 %)	< 0.001	6 (0.6 %)	49 (5.1 %)	< 0.001	9 (1.0 %)	24 (2.6 %)	0.01
Symptomatic VTE	6 (0.4 %)	11 (0.7 %)		3 (0.4 %)	15 (1.7 %)		8 (1.0 %)	24 (2.7 %)	
Major bleedings	6 (0.3 %)	2 (0.1 %)		1 (0.1 %)	1 (0.1 %)		7 (0.6 %)	6 (0.5 %)	

The analysis of the pooled results of the phase III studies corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

In addition to the phase III RECORD programme, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under real-life setting. Symptomatic VTE occurred in 57 (0.6 %) patients in the rivaroxaban group (n=8,778) and 88 (1.0 %) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomised studies.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.
Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator. For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

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

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to

12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

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

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.
The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.
In the Einstein DVT study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); Hazard Ratio HR: 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 ((95 % CI: 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3 % of the time for the mean treatment duration of 189 days, and 55.4 %, 60.1 %, and 62.8 % of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95 % CI: 0.35 - 1.35).

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

Table 5: Efficacy and safety results from phase III Einstein DVT

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dose and duration	**Rivaroxaban[a)]** **3, 6 or 12 months** **N=1,731**	**Enoxaparin/VKA[b)]** **3, 6 or 12 months** **N=1,718**
Symptomatic recurrent VTE*	36 (2.1 %)	51 (3.0 %)
Symptomatic recurrent PE	20 (1.2 %)	18 (1.0 %)
Symptomatic recurrent DVT	14 (0.8 %)	28 (1.6 %)
Symptomatic PE and DVT	1 (0.1 %)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2 %)	6 (0.3 %)
Major or clinically relevant non-major bleeding	139 (8.1 %)	138 (8.1 %)
Major bleeding events	14 (0.8 %)	20 (1.2 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); HR: 1.123 (0.749 –

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

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

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

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* p < 0.0026 (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749-1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 7).

Table 7: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE

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

Study population	**8,281 patients with an acute symptomatic DVT or PE**	
Treatment dose and duration	**Rivaroxaban[a)]** **3, 6 or 12 months** **N=4,150**	**Enoxaparin/VKA[b)]** **3, 6 or 12 months** **N=4,131**
Major or clinically relevant non-major bleeding	388 (9.4 %)	412 (10.0 %)
Major bleeding events	40 (1.0 %)	72 (1.7 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661-1.186)

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

In the Einstein Extension study (see Table 8) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

Table 8: Efficacy and safety results from phase III Einstein Extension

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

a) Rivaroxaban 20 mg once daily
* $p < 0.0001$ (superiority), HR: 0.185 (0.087-0.393)

In the Einstein Choice study (see Table 9) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

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

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**

Treatment dose	**Rivaroxaban 20 mg once daily N=1,107**	**Rivaroxaban 10 mg once daily N=1,127**	**ASA 100 mg once daily N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5 %) *	13 (1.2 %)* *	50 (4.4 %)
Symptomatic recurrent PE	6 (0.5 %)	6 (0.5 %)	19 (1.7 %)
Symptomatic recurrent DVT	9 (0.8 %)	8 (0.7 %)	30 (2.7 %)
Fatal PE/death where PE cannot be ruled out	2 (0.2 %)	0 (0.0 %)	2 (0.2 %)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7 %)	18 (1.6 %)	56 (5.0 %)
Major bleeding events	6 (0.5 %)	5 (0.4 %)	3 (0.3 %)
Clinically relevant non-major bleeding	30 (2.7 %)	22 (2.0 %)	20 (1.8 %)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1 %)$^{+}$	17 (1.5 %)$^{++}$	53 (4.7 %)

* $p < 0.001$(superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)
** $p < 0.001$ (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)
$^{+}$ Rivaroxaban 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)
$^{++}$ Rivaroxaban 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18-0.55), $p < 0.0001$ (nominal)

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

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

<u>Patients with high risk triple positive antiphospholipid syndrome</u>

In an investigator sponsored, randomised open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The trial

was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomised to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) <50 mL/min) and 61 to warfarin (INR 2.0- 3.0). Thromboembolic events occurred in 12% of patients randomised to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomised to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing rivaroxaban in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2-4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80-100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or Cmax at the 2.5 mg and 10 mg dose. Rivaroxaban 2.5 mg and 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from on the day of surgery and the following day when variability in exposure is high (70 %).
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29 % and 56 % decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

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

Biotransformation and elimination

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

Special populations

Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

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

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

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

Renal impairment
There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50-80 ml/min), moderate (creatinine clearance 30-49 ml/min) and severe (creatinine clearance 15-29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6-fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15-29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90 % prediction interval) 2-4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7-273) and 14 (4-51) mcg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

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

Paediatric population

Safety and efficacy have not been established in the indication primary prevention of VTE for children and adolescents up to 18 years.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating

Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple sauce for up to 4 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC/Aluminium blisters in cartons of 5, 10, 14, 28, 30, 98 or 100 film-coated tablets or perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.
HDPE bottle fitted with white opaque child resistant polypropylene closure and induction sealing liner wad. Pack size 30 or 90 film-coated tablets.
HDPE bottle fitted with white opaque continuous thread polypropylene screw closure and induction sealing liner wad. Pack size 500 film-coated tablets.

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.

Crushing of tablets
Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. Enteral feeding is not required immediately after administration of the 10 mg tablets.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/012-023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2020
Date of latest renewal: 6th August 2025

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 15 mg rivaroxaban.

Excipient with known effect

Each film-coated tablet contains 20.920 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Red coloured, round, biconvex, approximately 5.00 mm in diameter, film coated tablets debossed with ‘‘IL’’ on one side and ‘‘2’’ on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism in adults
The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Rivaroxaban Accord should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Rivaroxaban Accord immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

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

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with rivaroxaban 10 mg once daily, a dose of rivaroxaban 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	Time period	**Dosing schedule**	**Total daily dose**
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take Rivaroxaban Accord immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of VTE and prevention of VTE recurrence in children and adolescents
Rivaroxaban Accord treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1).

The dose for children and adolescent is calculated based on body weight.

- Body weight from 30 to 50 kg:
  a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight of 50 kg or more:
  a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of other medicinal products that contain rivaroxaban granules for oral suspension available on the market.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to rivaroxaban
- Prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.
- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:
  VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used (see section 4.5).

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

Paediatric patients:
Children who convert from Rivaroxaban Accord to VKA need to continue Rivaroxaban Accord for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Rivaroxaban Accord. Co-administration of Rivaroxaban Accord and VKA is advised to continue until the INR is ≥ 2.0. Once Rivaroxaban Accord is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

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

Converting from rivaroxaban to parenteral anticoagulants
Discontinue Rivaroxaban Accord and give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.

Special populations

Renal impairment
Adults:

Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Accord is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
In patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment the following dose recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2). When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

Paediatric population:
- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2): Rivaroxaban Accord is not recommended as no clinical data is available (see section 4.4).

Hepatic impairment
Rivaroxaban Accord 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 sections 4.3 and 5.2). No clinical data is available in children with hepatic impairment.

Elderly population
No dose adjustment (see section 5.2)

Body weight
No dose adjustment for adults (see section 5.2)
For paediatric patients the dose is determined based on body weight.

Gender
No dose adjustment (see section 5.2)

Patients undergoing cardioversion
Rivaroxaban Accord can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban Accord treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). For all patients, confirmation should be sought prior to cardioversion that the patient has taken Rivaroxaban Accord as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.
Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement

There is limited experience of a reduced dose of 15 mg rivaroxaban once daily (or 10 mg rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

Paediatric population
The safety and efficacy of Rivaroxaban Accord in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Method of administration

Adults
Rivaroxaban Accord is for oral use.
The tablets are to be taken with food (see section 5.2).

Crushing of tablets
For patients who are unable to swallow whole tablets, Rivaroxaban Accord tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban Accord 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban Accord tablet may also be given through gastric tubes *(see sections 5.2 and 6.6).*

Children and adolescents weighing 30 kg to 50 kg
Rivaroxaban Accord is for oral use.
The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

Crushing of tablets
For patients who are unable to swallow whole tablets, other medicinal products that contain rivaroxaban granules for oral suspension available on the market should be used.
If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.
The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

4.3 Contraindications

Hypersensitivity to the active substance 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.

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).

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

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

Haemorrhagic risk

As with other anticoagulants, patients taking Rivaroxaban Accord are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban Accord 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 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.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (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).

Paediatric population
There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk.
Rivaroxaban Accord is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

Rivaroxaban Accord should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).
Rivaroxaban Accord is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2), as no clinical data is available.

Interaction with other medicinal products

The use of Rivaroxaban Accord 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. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-gp (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), acetylsalicylic acid 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 section 4.5).

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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

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 rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Accord is not recommended for these patients.
Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy

in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/ transient ischaemic attack (TIA).

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

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. In particular 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.

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 15 mg rivaroxaban in these situations.
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. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.
No data is available on the timing of the placement or removal of neuraxial catheter in children while on Rivaroxaban Accord. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban Accord 15 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Rivaroxaban Accord 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

Increasing age may increase haemorrhagic risk (see section 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. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Rivaroxaban Accord 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 tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

CYP3A4 and P-gp inhibitors

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

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

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

CYP3A4 inducers

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

Other concomitant therapies

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

Laboratory parameters

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban Accord is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

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

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

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.

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

Indication	**Number of patients***	**Total daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1-21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

*Patients exposed to at least one dose of rivaroxaban
** From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	**Any bleeding**	**Anaemia**

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8 % of patients	5.9 % of patients
Prevention of venous thromboembolism in medically ill patients	12.6 % of patients	2.1 % of patients
Treatment of DVT, PE and prevention of recurrence	23 % of patients	1.6 % of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6 % of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.
** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied
*** A selective approach to adverse event collection was applied
# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

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

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic,		Anaphylactic reactions including	

Common	Uncommon	Rare	Very rare	Not known
	Angioedema and allergic oedema		anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				

Common	Uncommon	Rare	Very rare	Not known
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		
Investigations				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

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 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 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 bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see 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.

Paediatric population
Treatment of VTE and prevention of VTE recurrence
The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.
In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

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

In adults, rare cases of 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”). There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.
A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (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 in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (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 adults and in children 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 adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.
In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8-16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18-30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1-4 hours after tablet intake (i.e. at the

time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16-36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Paediatric population
PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti- Factor Xa tests in mcg/L (see table 13 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

Clinical efficacy and safety

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30-49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.
34.9 % of patients were treated with acetylsalicylic acid and 11.4 % were treated with class III antiarrhythmic including amiodarone.

Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71 % per year) and 241 on warfarin (2.16 % per year) (HR 0.79; 95 % CI, 0.66-0.96; P < 0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12 % per year) and 306 on warfarin (2.42 % per year) (HR 0.88; 95 % CI, 0.74-1.03; P < 0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 4.
Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55 % of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0-3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the Hazard Ration (HR) with rivaroxaban versus warfarin was 0.74 (95 % CI, 0.49-1.12).

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

Table 4: Efficacy results from phase III ROCKET AF

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

Table 5: Safety results from phase III ROCKET AF

Study population	**Patients with non-valvular atrial fibrillationa)**		
Treatment dose	**Rivaroxaban 20 mg once daily (15 mg once dailyin patients with moderate renal impairment)** **Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0)** **Event rate (100 pt-yr)**	**HR (95% CI)** **p-value**
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96-1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90-1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31-0.79) 0.003
Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53-0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47-0.93) 0.019
Haemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03-1.44) 0.019

Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01-1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96-1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70-1.02) 0.073

a) Safety population, on treatment
* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, noninterventional, open label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean CHADS2 score was 1.9 and HAS-BLED score was 2.0 in XANTUS, compared to a mean CHADS2 and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.
These observations in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 162,000 patients from four countries, rivaroxaban was prescribed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The event rate for ischaemic stroke was 0.70 (95% CI 0.44 - 1.13) per 100 patient-years. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.43 (95% CI 0.31 - 0.59) for intracranial bleeding, 1.04 (95% CI 0.65 - 1.66) for gastrointestinal bleeding, 0.41 (95% CI 0.31 - 0.53) for urogenital bleeding and 0.40 (95% CI 0.25 - 0.65) for other bleeding.

Patients undergoing cardioversion

A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the prevention of cardiovascular events. TEE- guided (1-5 days of pretreatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, myocardial infarction (MI) and cardiovascular death) occurred in 5 (0.5 %) patients in the rivaroxaban group (n = 978) and 5 (1.0 %) patients in the VKA group (n = 492; RR 0.50; 95 % CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6 %) and 4 (0.8 %) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

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

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.
Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30-49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus

DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30-49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose adjusted VKA plus low-dose ASA.
The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7 %), 117 (16.6 %), and 167 (24.0 %) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95 % CI 0.47-0.76; $p < 0.001$, and HR 0.63; 95 % CI 0.50-0.80; $p < 0.001$, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9 %), 36 (5.1 %), and 36 (5.2 %) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.
The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.
Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

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

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

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

In Einstein Choice, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed

anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomisation date (median: 351 days). Rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.
The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE.

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

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

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

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dose and duration	**Rivaroxaban[a)] 3, 6 or 12 months N=1,731**	**Enoxaparin/VKA[b)] 3, 6 or 12 months N=1,718**
Symptomatic recurrent VTE*	36 (2.1 %)	51 (3.0 %)
Symptomatic recurrent PE	20 (1.2 %)	18 (1.0 %)
Symptomatic recurrent DVT	14 (0.8 %)	28 (1.6 %)
Symptomatic PE and DVT	1 (0.1 %)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2 %)	6 (0.3 %)
Major or clinically relevant non-major bleeding	139 (8.1 %)	138 (8.1 %)
Major bleeding events	14 (0.8 %)	20 (1.2 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443-1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 7) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); HR: 1.123 (0.749-1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 ((95 % CI: 0.633-1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63 % of the time for the mean treatment duration of 215 days, and 57 %, 62 %, and 65 % of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the

level of mean centre TTR (Time in Target INR Range of 2.0-3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277-1.484).

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

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

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0026$ (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749-1.684)

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

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

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

Major bleeding events	40 (1.0 %)	72 (1.7 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* p < 0.0001 (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661-1.186)

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

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

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

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

a) Rivaroxaban 20 mg once daily
* p < 0.0001 (superiority), HR: 0.185 (0.087-0.393)

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

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

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**Rivaroxaban 20 mg once daily N=1,107**	**Rivaroxaban 10 mg once daily N=1,127**	**ASA 100 mg once daily N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5 %)*	13 (1.2 %)**	50 (4.4 %)

Study population	3,396 patients continued prevention of recurrent venous thromboembolism		
Treatment dose	**Rivaroxaban 20 mg once daily N=1,107**	**Rivaroxaban 10 mg once daily N=1,127**	**ASA 100 mg once daily N=1,131**
Symptomatic recurrent PE	6 (0.5 %)	6 (0.5 %)	19 (1.7 %)
Symptomatic recurrent DVT	9 (0.8 %)	8 (0.7 %)	30 (2.7 %)
Fatal PE/death where PE cannot be ruled out	2 (0.2 %)	0 (0.0 %)	2 (0.2 %)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7 %)	18 (1.6 %)	56 (5.0 %)
Major bleeding events	6 (0.5 %)	5 (0.4 %)	3 (0.3 %)
Clinically relevant non-major bleeding	30 (2.7 %)	22 (2.0 %)	20 (1.8 %)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1 %)$^{+}$	17 (1.5 %)$^{++}$	53 (4.7 %)

* $p < 0.001$(superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)
** $p < 0.001$ (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)
$^{+}$ Rivaroxaban 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)
$^{++}$ Rivaroxaban 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18-0.55), $p < 0.0001$ (nominal)

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

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

Paediatric population

Treatment of VTE and prevention of VTE recurrence in paediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less

than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).

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

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

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

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

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

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

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

Event	**Rivaroxaban N=335***	**Comparator N=165***
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)

Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

*FAS= full analysis set, all children who were randomised

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

	Rivaroxaban N=329*	**Comparator N=162***
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

* SAF= safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product.

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

Patients with high risk triple positive antiphospholipid syndrome

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing rivaroxaban in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The following information is based on the data obtained in adults.
Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2-4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80-100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.
Due to a reduced extent of absorption an oral bioavailability of 66 % was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.
Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29 % and 56 % decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Paediatric population
Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food. Rivaroxaban 15 mg tablets should be taken with feeding or with food (see section 4.2).

Distribution

Plasma protein binding in adults 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.

Paediatric population
No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. Vss estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is

dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

Biotransformation and elimination

In adults, 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.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives (t1/2) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

Special populations

Gender
In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Different weight categories
In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.
In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

Inter-ethnic differences
In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

Hepatic impairment
Cirrhotic adult 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).
No clinical data is available in children with hepatic impairment.

Renal impairment
In adults, 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).
No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90 % prediction interval) 2-4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22-535) and 32 (6-239) mcg/l, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 13.

Table 13: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age

Time intervals								

o.d.	**N**	**12 -< 18 years**	**N**	**6 -< 12 years**				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d.	**N**	**6 -< 12 years**	**N**	**2 -< 6 years**	**N**	**0.5 -< 2 years**		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
t.i.d.	**N**	**2 -< 6 years**	**N**	**Birth -< 2 years**	**N**	**0.5 -< 2 years**	**N**	**Birth -< 0.5 years**
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated
Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5-30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 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 have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.
Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.
In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre-and postnatal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams. Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating

Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC/Aluminium blisters in cartons of 10, 14, 28, 30, 42, 48, 56, 90, 98 or 100 film-coated tablets or perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.
HDPE bottle fitted with white opaque child resistant polypropylene closure and induction sealing liner wad. Pack size 30 or 90 film-coated tablets.
HDPE bottle fitted with white opaque continuous thread polypropylene screw closure and induction sealing liner wad. Pack size 500 film-coated tablets.

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.

Crushing of tablets

Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/024-038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2020
Date of latest renewal: 6th August 2025

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg rivaroxaban.

Excipient with known effect

Each film-coated tablet contains 27.90 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Dark red coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with ‘‘IL3’’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism in adults
The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Rivaroxaban Accord should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding (see section 4.4).

If a dose is missed the patient should take Rivaroxaban Accord immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

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

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Accord 10 mg once daily, a dose of Rivaroxaban Accord 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	Time period	**Dosing schedule**	**Total daily dose**
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Rivaroxaban Accord for treatment of DVT/PE is available.

If a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take Rivaroxaban Accord immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of VTE and prevention of VTE recurrence in children and adolescents
Rivaroxaban Accord treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section 5.1).

The dose for children and adolescent is calculated based on body weight.
- Body weight of 50 kg or more:
  a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg:
  a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of other medicinal products that contain rivaroxaban granules for oral suspension available on the market.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.
Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to rivaroxaban
- Prevention of stroke and systemic embolism, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.
- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:
  VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used (see section 4.5).

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

Paediatric patients:
Children who convert from Rivaroxaban Accord to VKA need to continue Rivaroxaban Accord for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Rivaroxaban Accord. Co-administration of Rivaroxaban Accord and VKA is advised to continue until the INR is ≥ 2.0. Once Rivaroxaban Accord is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section 4.5).

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

Converting from rivaroxaban to parenteral anticoagulants
Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.

Special populations

Renal impairment
Adults:
Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Accord is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment the following dose recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2). When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

Paediatric population:
- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m^2): no dose adjustment is required, based on data in adults and limited data in paediatric patients (see section 5.2).
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2): Rivaroxaban Accord is not recommended as no clinical data is available (see section 4.4).

Hepatic impairment
Rivaroxaban Accord 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 sections 4.3 and 5.2). No clinical data is available in children with hepatic impairment.

Elderly population
No dose adjustment (see section 5.2)

Body weight
No dose adjustment for adults (see section 5.2)
For paediatric patients the dose is determined based on body weight.

Gender
No dose adjustment (see section 5.2)

Patients undergoing cardioversion
Rivaroxaban Accord can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban Accord treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). For all patients,

confirmation should be sought prior to cardioversion that the patient has taken Rivaroxaban Accord as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement
There is limited experience of a reduced dose of 15 mg rivaroxaban once daily (or 10 mg rivaroxaban once daily for patients with moderate renal impairment [creatinine clearance 30-49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

Paediatric population
The safety and efficacy of Rivaroxaban Accord in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Method of administration

Adults
Rivaroxaban Accord is for oral use.
The tablets are to be taken with food (see section 5.2).

Crushing of tablets
For patients who are unable to swallow whole tablets, Rivaroxaban Accord tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rivaroxaban Accord 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed Rivaroxaban Accord tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

Children and adolescents weighing more than 50 kg
Rivaroxaban Accord is for oral use.
The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section 5.2). The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

Crushing of tablets
For patients who are unable to swallow whole tablets, other medicinal products that contain rivaroxaban granules for oral suspension available on the market should be used. If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.
The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections 5.2 and 6.6).

4.3 Contraindications

Hypersensitivity to the active substance 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.

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).

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

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

Haemorrhagic risk

As with other anticoagulants, patients taking Rivaroxaban Accord are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban Accord 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 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.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (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).

Paediatric population
There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk.
Rivaroxaban Accord is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).
Rivaroxaban Accord should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).
Rivaroxaban Accord is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is available.

Interaction with other medicinal products

The use of Rivaroxaban Accord 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. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (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), acetylsalicylic acid 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 section 4.5).

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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

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 rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban

provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Accord is not recommended for these patients.

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

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/ transient ischaemic attack (TIA).

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

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. In particular 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.

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 20 mg rivaroxaban in these situations.
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. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.
No data is available on the timing of the placement or removal of neuraxial catheter in children while on Rivaroxaban Accord. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban Accord 20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban Accord 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

Increasing age may increase haemorrhagic risk (see section 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. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Rivaroxaban Accord 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 tablet, that is to say essentially "sodium- free".

4.5 Interaction with other medicinal products and other forms of interaction

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

CYP3A4 and P-gp inhibitors

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

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On

the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

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

Other concomitant therapies

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

Laboratory parameters

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of rivaroxaban have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, rivaroxaban is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Rivaroxaban has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8).

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

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

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.

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

Indication	**Number of patients***	**Total daily dose**	**Maximum treatment duration**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1-21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight- adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an acute coronary syndrome (ACS)	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

*Patients exposed to at least one dose of rivaroxaban
** From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8 % of patients	5.9 % of patients
Prevention of venous thromboembolism in medically ill patients	12.6 % of patients	2.1 % of patients
Treatment of DVT, PE and prevention of recurrence	23 % of patients	1.6 % of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6 % of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.
** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied
*** A selective approach to adverse event collection was applied
# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

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

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective	Thrombocytosis (incl. platelet			

Common	Uncommon	Rare	Very rare	Not known
laboratory parameters)	count increased)[A], Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash,	Urticaria		Stevens-Johnson syndrome/ Toxic Epidermal	

Common	Uncommon	Rare	Very rare	Not known
ecchymosis, cutaneous and subcutaneous haemorrhage			Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)				Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		
Investigations				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

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 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 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 bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see 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.

Paediatric population
Treatment of VTE and prevention of VTE recurrence
The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.
In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

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

In adults, rare cases of 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"). There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.
A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (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 in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter (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 adults and in children 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 adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.
In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e. at the time of maximum effect) for

15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8-16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18-30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1-4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16-36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Paediatric population
PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L (see table 13 in section 5.2 for ranges of observed rivaroxaban plasma concentrations in children). The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

Clinical efficacy and safety

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to rivaroxaban 20 mg once daily (15 mg once daily in patients with creatinine clearance 30-49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months. 34.9 % of patients were treated with acetylsalicylic acid and 11.4 % were treated with class III antiarrhythmic including amiodarone.

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

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55 % of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0-3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the Hazard Ration (HR) with rivaroxaban versus warfarin was 0.74 (95 % CI, 0.49-1.12).
The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 5).

Table 4: Efficacy results from phase III ROCKET AF

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

Table 5: Safety results from phase III ROCKET AF

Study population	**Patients with non-valvular atrial fibrillationa)**		
Treatment dose	**Rivaroxaban 20 mg once daily (15 mg once daily in patients with moderate renal impairment) Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)**	**HR (95% CI) p-value**
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96-1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90-1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31-0.79) 0.003

Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53-0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47-0.93) 0.019
Haemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03-1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01-1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96-1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70-1.02) 0.073

a) Safety population, on treatment
* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, noninterventional, open label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,704 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean CHADS2 score was 1.9 and HAS-BLED score was 2.0 in XANTUS, compared to a mean CHADS2 and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.
These observations in clinical practice are consistent with the established safety profile in this indication.

In a post-authorisation, non-interventional study, in more than 162,000 patients from four countries, rivaroxaban was prescribed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The event rate for ischaemic stroke was 0.70 (95% CI 0.44 - 1.13) per 100 patient-years. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.43 (95% CI 0.31 - 0.59) for intracranial bleeding, 1.04 (95% CI 0.65 - 1.66) for gastrointestinal bleeding, 0.41 (95% CI 0.31 - 0.53) for urogenital bleeding and 0.40 (95% CI 0.25 - 0.65) for other bleeding.

Patients undergoing cardioversion

A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the prevention of cardiovascular events. TEE- guided (1-5 days of pretreatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, myocardial infarction (MI) and cardiovascular death) occurred in 5 (0.5 %) patients in the rivaroxaban group (n = 978) and 5 (1.0 %) patients in the VKA group (n = 492; RR 0.50; 95 % CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6 %) and 4 (0.8 %) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95 % CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

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

A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded.
Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30-49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30-49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose adjusted VKA plus low-dose ASA.
The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7 %), 117 (16.6 %), and 167 (24.0 %) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95 % CI 0.47-0.76; $p < 0.001$, and HR 0.63; 95 % CI 0.50-0.80; $p < 0.001$, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9 %), 36 (5.1 %), and 36 (5.2 %) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.
The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.
Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

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

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

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

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

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

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

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

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dose and duration	**Rivaroxaban[a] 3, 6 or 12 months N=1,731**	**Enoxaparin/VKA[b] 3, 6 or 12 months N=1,718**
Symptomatic recurrent VTE*	36 (2.1 %)	51 (3.0 %)
Symptomatic recurrent PE	20 (1.2 %)	18 (1.0 %)
Symptomatic recurrent DVT	14 (0.8 %)	28 (1.6 %)
Symptomatic PE and DVT	1 (0.1 %)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2 %)	6 (0.3 %)
Major or clinically relevant non-major bleeding	139 (8.1 %)	138 (8.1 %)
Major bleeding events	14 (0.8 %)	20 (1.2 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443-1.042), p=0.076 (superiority)

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

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

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

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* p < 0.0026 (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749-1.684)

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

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

Study population	**8,281 patients with an acute symptomatic DVT or PE**	
Treatment dose and duration	**Rivaroxaban[a)] 3, 6 or 12 months N=4,150**	**Enoxaparin/VKA[b)] 3, 6 or 12 months N=4,131**
Symptomatic recurrent VTE*	86 (2.1 %)	95 (2.3 %)
Symptomatic recurrent PE	43 (1.0 %)	38 (0.9 %)

Symptomatic recurrent DVT	32 (0.8 %)	45 (1.1 %)
Symptomatic PE and DVT	1 (<0.1 %)	2 (<0.1 %)
Fatal PE/death where PE cannot be ruled out	15 (0.4 %)	13 (0.3 %)
Major or clinically relevant non-major bleeding	388 (9.4 %)	412 (10.0 %)
Major bleeding events	40 (1.0 %)	72 (1.7 %)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* p < 0.0001 (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661-1.186)

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

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

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

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

a) Rivaroxaban 20 mg once daily
* p < 0.0001 (superiority), HR: 0.185 (0.087-0.393)

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

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

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**Rivaroxaban 20 mg once daily N=1,107**	**Rivaroxaban 10 mg once daily N=1,127**	**ASA 100 mg once daily N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5 %) *	13 (1.2 %)* *	50 (4.4 %)
Symptomatic recurrent PE	6 (0.5 %)	6 (0.5 %)	19 (1.7 %)
Symptomatic recurrent DVT	9 (0.8 %)	8 (0.7 %)	30 (2.7 %)
Fatal PE/death where PE cannot be ruled out	2 (0.2 %)	0 (0.0 %)	2 (0.2 %)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7 %)	18 (1.6 %)	56 (5.0 %)
Major bleeding events	6 (0.5 %)	5 (0.4 %)	3 (0.3 %)
Clinically relevant non-major bleeding	30 (2.7 %)	22 (2.0 %)	20 (1.8 %)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1 %)$^{+}$	17 (1.5 %)$^{++}$	53 (4.7 %)

* $p < 0.001$(superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)
** $p < 0.001$ (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)
$^{+}$ Rivaroxaban 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)
$^{++}$ Rivaroxaban 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18-0.55), $p < 0.0001$ (nominal)

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

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

Paediatric population

Treatment of VTE and prevention of VTE recurrence in paediatric patients

A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study (see section 5.2).
The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE.

There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; 90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; 74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; 171/335 patients in the rivaroxaban group, 85/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non-CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35 (50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

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

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

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

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

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

Event	**Rivaroxaban N=335***	**Comparator N=165***
Recurrent VTE (primary efficacy outcome)	4	5

	(1.2%, 95% CI 0.4% – 3.0%)	(3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Composite: Symptomatic recurrent VTE + major bleeding (net clinical benefit)	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)
Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

* FAS= full analysis set, all children who were randomised

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

	Rivaroxaban N=329*	**Comparator N=162***
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

* SAF = safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product

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

Patients with high risk triple positive antiphospholipid syndrome

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with the reference medicinal product containing rivaroxaban in all subsets of the paediatric population in the prevention of thromboembolic events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The following information is based on the data obtained in adults.
Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2-4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80-100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.
Due to a reduced extent of absorption an oral bioavailability of 66 % was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.
Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29 % and 56 % decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Paediatric population
Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food. Rivaroxaban 20 mg tablets should be taken with feeding or with food (see section 4.2).

Distribution

Plasma protein binding in adults 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.

Paediatric population

No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. Vss estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

Biotransformation and elimination

In adults, 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.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives (t1/2) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

Special populations

Gender
In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients. An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Different weight categories
In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.
In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

Inter-ethnic differences
In adults, no clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

Hepatic impairment
Cirrhotic adult 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).
No clinical data is available in children with hepatic impairment.

Renal impairment
In adults, 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).
No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90 % prediction interval) 2-4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22-535) and 32 (6-239) mcg/l, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 13.

Table 13: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age

Time intervals								
o.d.	**N**	**12 - < 18 years**	**N**	**6 -< 12 years**				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d.	**N**	**6 -< 12 years**	**N**	**2 -< 6 years**	**N**	**0.5 -< 2 years**		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
t.i.d.	**N**	**2 -< 6 years**	**N**	**Birth - < 2 years**	**N**	**0.5 -< 2 years**	**N**	**Birth - < 0.5 years**
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated
Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5-30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 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 have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

5.3 Preclinical safety data

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

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E55)
Magnesium stearate (E572)

Film-coating

Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC/Aluminium blisters in cartons of 10, 14, 28, 30, 42, 56, 90, 98 or 100 film-coated tablets or perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.
HDPE bottle fitted with white opaque child resistant polypropylene closure and induction sealing liner wad. Pack size 30 or 90 film-coated tablets.
HDPE bottle fitted with white opaque continuous thread polypropylene screw closure and induction sealing liner wad. Pack size 500 film-coated tablets.

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.

Crushing of tablets
Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/040-053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2020
Date of latest renewal: 6th August 2025

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg film-coated tablets
Rivaroxaban Accord 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mg film-coated tablet contains 15 mg rivaroxaban.
Each 20 mg film-coated tablet contains 20 mg rivaroxaban.

Excipient with known effect

Each 15 mg film-coated tablet contains 20.92 mg lactose (as monohydrate), see section 4.4.
Each 20 mg film-coated tablet contains 27.90 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Rivaroxaban Accord 15 mg: Red coloured, round, biconvex, approximately 5.00 mm in diameter, film coated tablets debossed with ‘‘IL’’ on one side and ‘‘2’’ on other side.
Rivaroxaban Accord 20 mg: Dark red coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with ‘‘IL3’’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

4.2 Posology and method of administration

Posology

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

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Rivaroxaban Accord 10 mg once daily, a dose of Rivaroxaban Accord 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	Time period	**Dosing schedule**	**Total daily dose**
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

The 4-week treatment initiation pack of Rivaroxaban Accord is dedicated to patients who will transition from 15 mg twice daily to 20 mg once daily from Day 22 onwards (see section 6.5).
For patients with moderate or severe renal impairment where the decision has been taken for 15 mg once daily from Day 22 onwards, other pack sizes only containing 15 mg film-coated tablets are available (see dosing instructions in section "Special populations" below).

If a dose is missed during the 15 mg twice daily treatment phase (day 1-21), the patient should take Rivaroxaban Accord immediately to ensure intake of 30 mg rivaroxaban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Rivaroxaban Accord immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to rivaroxaban
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rivaroxaban Accord therapy should be initiated once the International Normalised Ration (INR) is ≤ 2.5.
When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used (see section 4.5).

Converting from rivaroxaban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.
In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is ≥ 2.0.
For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both rivaroxaban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once Rivaroxaban Accord 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 rivaroxaban
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start rivaroxaban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

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

Special populations

Renal impairment
Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban Accord is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

In patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment the following dose recommendations apply:

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg twice daily for the first 3 weeks.
  Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 4.4, 5.1 and 5.2). When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

Hepatic impairment
Rivaroxaban Accord 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 sections 4.3 and 5.2).

Elderly population
No dose adjustment (see section 5.2)

Body weight
No dose adjustment (see section 5.2)

Gender
No dose adjustment (see section 5.2)

Paediatric population
Rivaroxaban Accord treatment initiation pack should not be used in children aged 0 to 18 years because it is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

Method of administration

Rivaroxaban Accord is for oral use.
The tablets are to be taken with food (see section 5.2).

Crushing of tablets
For patients who are unable to swallow whole tablets, Rivaroxaban Accord tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the

administration of crushed Rivaroxaban Accord 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed tablet may also be given through gastric tubes (see sections 5.2 and 6.6).

4.3 Contraindications

Hypersensitivity to the active substance 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.

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).

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

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

Haemorrhagic risk
As with other anticoagulants, patients taking Rivaroxaban Accord are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban Accord 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 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.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (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. Rivaroxaban Accord is to be used with caution in patients with creatinine clearance 15-29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). Rivaroxaban Accord should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicinal products

The use of Rivaroxaban Accord 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), acetylsalicylic acid 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 section 4.5).

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban 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

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 rivaroxaban is contraindicated (see section 4.3).

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban Accord 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. In particular 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.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

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

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 15 mg or 20 mg rivaroxaban in these situations.
To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) 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. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban Accord 15/20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban Accord 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

Increasing age may increase haemorrhagic risk (see section 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. Rivaroxaban should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Rivaroxaban Accord 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 tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and P-gp inhibitors

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

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

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

CYP3A4 inducers

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

Other concomitant therapies

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

Laboratory parameters

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy of rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy (see section 4.3).
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of rivaroxaban have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, rivaroxaban is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen pivotal phase III studies (see Table 1).

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.

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

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of VTE in medically ill patients	3,997	10 mg	39 days
Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight-adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of atherothrombotic events in patients after an acute coronary syndrome (ACS)	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
	3,256**	5 mg co-administered with ASA	42 months

*Patients exposed to at least one dose of rivaroxaban
** From the VOYAGER PAD study

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see also section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients

Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
	8.38 per 100 patient years #	0.74 per 100 patient years*** #

* For all rivaroxaban studies all bleeding events are collected, reported and adjudicated.
** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied
*** A selective approach to adverse event collection was applied
# From the VOYAGER PAD study

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.

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

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post marketing use* and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A], Thrombocytopenia			
Immune system disorders				
	Allergic reaction, dermatitis allergic, Angioedema and allergic oedema		Anaphylactic reactions including anaphylactic shock	
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			
Eye disorders				

Common	Uncommon	Rare	Very rare	Not known
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis			Eosinophilic pneumonia	
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
Increase in transaminases	Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]	Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS syndrome	
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		Compartment syndrome secondary to a bleeding
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal				Renal failure/acute renal failure secondary to a

Common	Uncommon	Rare	Very rare	Not known
impairment (incl. blood creatinine increased, blood urea increased)				bleeding sufficient to cause hypoperfusion, Anticoagulant-related nephropathy
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		
Investigations				
	Increased LDH[A], increased lipase[A], increased amylase[A]			
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]		Vascular pseudoaneurysm[C]		

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)
* A pre-specified selective approach to adverse event collection was applied in selected phase III studies. The incidence of adverse reactions did not increase and no new adverse drug reaction was identified after analysis of these studies.

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 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 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 bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see 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.

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

Rare cases of 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"). Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01

Mechanism of action

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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.
In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.
In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).
The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

Clinical efficacy and safety

Treatment of DVT, PE and prevention of recurrent DVT and PE
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT and PE and prevention of recurrence.
Over 12,800 patients were studied in four randomised controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and Einstein Choice) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.

In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.
For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

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

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

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

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

In the Einstein DVT study (see Table 4) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); Hazard Ratio (HR): 0.680 (0.443 - 1.042), p=0.076 (test for superiority)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.67 ((95% CI: 0.47 - 0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35 - 1.35).

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

Table 4: Efficacy and safety results from phase III Einstein DVT

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dose and duration	**Rivaroxaban[a)] 3, 6 or 12 months N=1,731**	**Enoxaparin/VKA[b)] 3, 6 or 12 months N=1,718**
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 2.0); HR: 0.680 (0.443 - 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 5) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); hazard ratio: 1.123 (0.749 - 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the HR with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

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

Table 5: Efficacy and safety results from phase III Einstein PE

Study population	**4,832 patients with an acute symptomatic PE**	
Treatment dose and duration	**Rivaroxaban[a)] 3, 6 or 12 months N=2,419**	**Enoxaparin/VKA[b)] 3, 6 or 12 months N=2,413**
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0026$ (non-inferiority to a prespecified HR of 2.0); HR: 1.123 (0.749-1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 6).

Table 6: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE

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

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified HR of 1.75); HR: 0.886 (0.661 - 1.186)

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

In the Einstein Extension study (see Table 7) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

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

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

a) Rivaroxaban 20 mg once daily
* $p < 0.0001$ (superiority), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (see Table 8) rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

Table 8: Efficacy and safety results from phase III Einstein Choice

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**Rivaroxaban 20 mg once daily N=1,107**	**Rivaroxaban 10 mg once daily N=1,127**	**ASA 100 mg od N=1,131**
Treatment duration median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186 362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)
Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0 (0.0%)	2 (0.2%)
Symptomatic recurrent VTE, MI, stroke, or non- CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7%)	22 (2.0%)	20 (1.8%)

Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

* →p<0.001(superiority) rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20-0.59)
** →p<0.001 (superiority) rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14-0.47)
+ →Rivaroxaban 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27-0.71), p=0.0009 (nominal)
++ →Rivaroxaban 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18-0.55), p<0.0001 (nominal)

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

In a post-authorisation, non-interventional study, in more than 40,000 patients without a history of cancer from four countries, rivaroxaban was prescribed for the treatment or prevention of DVT and PE. The event rates per 100 patient-years for symptomatic/clinically apparent VTE/thromboembolic events leading to hospitalisation ranged from 0.64 (95% CI 0.40 - 0.97) in the UK to 2.30 (95% CI 2.11 - 2.51) for Germany. Bleeding resulting in hospitalisation occurred at event rates per 100 patient-years of 0.31 (95% CI 0.23 - 0.42) for intracranial bleeding, 0.89 (95% CI 0.67 - 1.17) for gastrointestinal bleeding, 0.44 (95% CI 0.26 - 0.74) for urogenital bleeding and 0.41 (95% CI 0.31 - 0.54) for other bleeding.

Patients with high risk triple positive antiphospholipid syndrome

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

Paediatric population

Rivaroxaban Accord treatment initiation pack is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

5.2 Pharmacokinetic properties

Absorption

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

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.
Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg are to be taken with food (see section 4.2).
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.
Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.
Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.
Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Distribution

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

Biotransformation and elimination

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

Special populations

Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

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

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

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

Renal impairment
There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6-fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.
Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

Pharmacokinetic data in patients

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) mcg/l, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated

after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 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

Rivaroxaban Accord treatment initiation pack is specifically designed for treatment of adult patients and is not appropriate for use in paediatric patients.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating

Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Treatment initiation pack for the first 4 weeks of treatment:
Clear PVC/Aluminium blisters in a wallet containing 49 film-coated tablets:
42 film-coated tablets Rivaroxaban Accord 15 mg and 7 film-coated tablets Rivaroxaban Accord 20 mg.

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.

Crushing of tablets
Rivaroxaban tablets may be crushed and suspended in 50 mL of water and administered via a nasogastric tube or gastric feeding tube after confirming gastric placement of the tube. Afterwards, the tube should be flushed with water. Since rivaroxaban absorption is dependent on the site of active substance release, administration of rivaroxaban distal to the stomach should be avoided, as this can result in reduced absorption and thereby, reduced active substance exposure. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th November 2020
Date of latest renewal: 6th August 2025

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Polska Sp. z o.o.
Ul. Lutomierska 50,
95-200 Pabianice, Poland

Pharmadox Healthcare Limited
KW20A Kordin Industrial Park, Paola
PLA 3000, Malta

Laboratori Fundació DAU
C/ C, 12-14 Pol. Ind. Zona Franca,
08040 Barcelona, Spain

Accord Healthcare B.V
Winthontlaan 200, 3526KV Utrecht,
Netherland

Accord Healthcare single member S.A.
64th Km National Road Athens,
Lamia, Schimatari, 32009, Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Rivaroxaban Accord. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Rivaroxaban Accord and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - The need for intake of the 15 mg and 20 mg tablets with food
  - Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
  - The need to inform Health Care Professionals that they are taking Rivaroxaban Accord if they need to have any surgery or invasive procedure.

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 2.5 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
56 film-coated tablets
98 film-coated tablets
100 film-coated tablets
168 film-coated tablets
196 film-coated tablets
10 x 1 film-coated tablets
100 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/001-008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 2.5 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 2.5 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER PACK (10 x 1 TABLETS, 100 x 1 TABLETS) FOR 2.5 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER FOR 2.5 MG (14 TABLETS CALENDAR PACK)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 2.5 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 2.5 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2.5 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain (only applicable for outer carton, not applicable for bottle label)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/009-011 (only applicable for outer carton, not applicable for bottle label)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 2.5 mg (only applicable for outer carton, not applicable for bottle label)

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC (only applicable for outer carton, not applicable for bottle label)
SN (only applicable for outer carton, not applicable for bottle label)
NN (only applicable for outer carton, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 10 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

5 film-coated tablets
10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
98 film-coated tablets
100 film-coated tablets
10 x 1 film-coated tablets
100 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/012-020

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 10 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 10 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER PACK (10 x 1 TABLETS, 100 x 1 TABLETS) FOR 10 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 10 MG (14 TABLETS CALENDAR PACK)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 10 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 10 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 10 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain (only applicable for outer carton, not applicable for bottle label)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/021-023 (only applicable for outer carton, not applicable for bottle label)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 10 mg (only applicable for outer carton, not applicable for bottle label)

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC (only applicable for outer carton, not applicable for bottle label)
SN (only applicable for outer carton, not applicable for bottle label)
NN (only applicable for outer carton, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 15 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
42 film-coated tablets
48 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
10 x 1 film-coated tablets
100 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/024-035

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 15 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 15 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER PACK (10 x 1 TABLETS, 100 x 1 TABLETS) FOR 15 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 15 MG (14 TABLETS CALENDAR PACK)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 15 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 15 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain (only applicable for outer carton, not applicable for bottle label)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/036-038 (only applicable for outer carton, not applicable for bottle label)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 15 mg (only applicable for outer carton, not applicable for bottle label)

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC (only applicable for outer carton, not applicable for bottle label)
SN (only applicable for outer carton, not applicable for bottle label)
NN (only applicable for outer carton, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 20 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
42 film-coated tablets
56 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
10 x 1 film-coated tablets
100 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/040-050

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 20 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 20 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER PACK (10 x 1 TABLETS, 100 x 1 TABLETS) FOR 20 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER FOR 20 MG (14 TABLETS CALENDAR PACK)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg tablets
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon.
Tue.
Wed.
Thu.
Fri.
Sat.
Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND LABEL FOR HDPE BOTTLE FOR 20 MG

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 20 mg film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 20 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets
500 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain (only applicable for outer carton, not applicable for bottle label)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/051-053 (only applicable for outer carton, not applicable for bottle label)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 20 mg (only applicable for outer carton, not applicable for bottle label)

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included. (only applicable for outer carton, not applicable for bottle label)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC (only applicable for outer carton, not applicable for bottle label)
SN (only applicable for outer carton, not applicable for bottle label)
NN (only applicable for outer carton, not applicable for bottle label)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF TREATMENT INITIATION PACK (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG) (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg
Rivaroxaban Accord 20 mg
film-coated tablets

rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each red film-coated tablet for week 1, 2 and 3 contains 15 mg rivaroxaban.
Each dark red film-coated tablet for week 4 contains 20 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack of 49 film-coated tablets contains:
42 film-coated tablets of 15 mg rivaroxaban
7 film-coated tablets of 20 mg rivaroxaban

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Treatment Initiation Pack

This treatment initiation pack is only for the first 4 weeks of treatment.

DOSE
Day 1 to 21: One 15 mg tablet twice a day (one 15 mg tablet in the morning and one in the evening) together with food.
From Day 22: One 20 mg tablet once a day (taken at same time each day) together with food.

Day 1 to 21: 15 mg 1 tablet twice a day (one 15 mg tablet in the morning and one in the evening) together with food.
From Day 22: 20 mg 1 tablet once a day (taken at same time each day) together with food.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1488/039

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivaroxaban Accord 15 mg
Rivaroxaban Accord 20 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

WALLET OF TREATMENT INITIATION PACK (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG) (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg
Rivaroxaban Accord 20 mg
film-coated tablets
rivaroxaban

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each red film-coated tablet for week 1, 2 and 3 contains 15 mg rivaroxaban.
Each dark red film-coated tablet for week 4 contains 20 mg rivaroxaban.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Each pack of 49 film-coated tablets contains:
42 film-coated tablets of 15 mg rivaroxaban
7 film-coated tablets of 20 mg rivaroxaban

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Treatment Initiation Pack

This treatment initiation pack is only for the first 4 weeks of treatment.

Day 1 to 21: 15 mg 1 tablet twice a day (one 15 mg tablet in the morning and one in the evening) together with food.
From Day 22: 20 mg 1 tablet once a day (taken at same time each day) together with food.

DOSE and DOSING SCHEME
Day 1 to 21: One 15 mg tablet twice a day (one 15 mg tablet in the morning and one in the evening).
From Day 22: One 20 mg tablet once a day (taken at same time each day).

Initial treatment Rivaroxaban Accord 15 mg twice a day First 3 weeks
Continuous treatment Rivaroxaban Accord 20 mg once a day Week 4 onwards Visit your doctor to ensure continued treatment.
To be taken with food.

Rivaroxaban Accord 15 mg
Start of therapy
15 mg
twice a day
Start date
WEEK 1, WEEK 2, WEEK 3
DAY 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

sun as symbol
moon as symbol

Dose change
Rivaroxaban Accord 20 mg
20 mg
once a day
taken at same time each day
Date of dose change
WEEK 4
DAY 22 DAY 23 DAY 24 DAY 25 DAY 26 DAY 27 DAY 28

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n, Edifici Est, 6ª Planta,
Barcelona, 08039
Spain

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER - 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF TREATMENT INITIATION PACK IN WALLET (42 FILM-COATED TABLETS OF 15 MG AND 7 FILM-COATED TABLETS OF 20 MG)

1. NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Accord 15 mg
Rivaroxaban Accord 20 mg
rivaroxaban

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT ALERT CARD

Patient Alert Card
Accord

Rivaroxaban Accord **2.5 mg** (tick box to tick the prescribed dose)
Rivaroxaban Accord **10 mg** (tick box to tick the prescribed dose)
Rivaroxaban Accord **15 mg** (tick box to tick the prescribed dose)
Rivaroxaban Accord **20 mg** (tick box to tick the prescribed dose)

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

I am under anticoagulation treatment with Rivaroxaban Accord (rivaroxaban)
Name:
Address:
Birth date:
Weight:
Other medicines / conditions:

In case of emergency, please notify:
Doctor's name:
Doctor's phone:
Doctor's stamp:

Please also notify:
Name:
Phone:
Relationship:

Information for health care providers:
- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Rivaroxaban Accord.

What should I know about Rivaroxaban Accord?
- Rivaroxaban Accord thins the blood, which prevents you from getting dangerous blood clots.
- Rivaroxaban Accord must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, **never skip a dose.**
- You must not stop taking Rivaroxaban Accord without first talking to your doctor as your risk of blood clots may increase.
- Tell your health care provider about any other medicines you are currently taking, took recently or intend to start taking, before you start Rivaroxaban Accord.
- Tell your health care provider that you are taking Rivaroxaban Accord before any surgery or invasive procedure.

When should I seek advice from my health care provider?
When taking a blood thinner such as Rivaroxaban Accord it is important to be aware of its possible side effects.
Bleeding is the most common side effect. Do not start taking Rivaroxaban Accord if you know you are at risk of bleeding, without first discussing this with your doctor. Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:
- pain
- swelling or discomfort
- headache, dizziness or weakness

- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- blood in your urine which may be pink or brown, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds

How do I take Rivaroxaban Accord?

- To ensure optimal protection, Rivaroxaban Accord
  - 2.5 mg can be taken with or without food
  - 10 mg can be taken with or without food
  - 15 mg must be taken with food
  - 20 mg must be taken with food

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Rivaroxaban Accord 2.5 mg film-coated tablets
rivaroxaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivaroxaban Accord is and what it is used for

You have been given Rivaroxaban Accord because

- you have been diagnosed with an acute coronary syndrome (a group of conditions that includes heart attack and unstable angina, a severe type of chest pain) and have been shown to have had an increase in certain cardiac blood tests.
  Rivaroxaban Accord reduces the risk in adults of having another heart attack or reduces the risk of dying from a disease related to your heart or your blood vessels.
  Rivaroxaban Accord will not be given to you on its own. Your doctor will also tell you to take either:
  - acetylsalicylic acid or
  - acetylsalicylic acid plus clopidogrel or ticlopidine.

  or

- you have been diagnosed with a high risk of getting a blood clot due to a coronary artery disease or peripheral artery disease which causes symptoms. Rivaroxaban Accord reduces the risk in adults of getting blot clots (atherothrombotic events). Rivaroxaban Accord will not be given to you on its own. Your doctor will also tell you to take acetylsalicylic acid. In some cases, if you get Rivaroxaban Accord after a procedure to open a narrowed or closed artery of your leg to restore blood flow, your doctor may also prescribe clopidogrel for you to take in addition to acetylsalicylic acid for a short while.

Rivaroxaban Accord contains the active substance rivaroxaban and belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

2. What you need to know before you take Rivaroxaban Accord

Do not take Rivaroxaban Accord

- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open
- if you have an acute coronary syndrome and previously had a bleeding or a blood clot in your brain (stroke)
- if you have coronary artery disease or peripheral artery disease and previously had a bleeding in your brain (stroke) or where there was a blockage of the small arteries providing blood to the brain's deep tissues (lacunar stroke) or if you had a blood clot in your brain (ischaemic, non-lacunar stroke) in the previous month
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast feeding

Do not take **Rivaroxaban Accord and tell your doctor** if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before taking Rivaroxaban Accord.
Rivaroxaban Accord should not be used in combination with certain other medicines which reduce blood clotting such as prasugrel or ticagrelor other than acetylsalicylic acid and clopidogrel/ticlopidine.

Take special care with Rivaroxaban Accord
- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section 'Other medicines and Rivaroxaban Accord')
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet), e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
  - you are older than 75 years
  - you weigh less than 60 kg
  - you have a coronary artery disease with severe symptomatic heart failure
- if you have a prosthetic heart valve
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If any of the above apply to you, tell your doctor before you take Rivaroxaban Accord. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If you need to have an operation:

- it is very important to take Rivaroxaban Accord before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
    - it is very important to take Rivaroxaban Accord before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
    - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

Children and adolescents
Rivaroxaban Accord is not recommended for people under 18 years of age. There is not enough information on its use in children and adolescents.

Other medicines and Rivaroxaban Accord
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
- If you are taking**:**
    - some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
    - ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
    - some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
    - some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
    - other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol prasugrel and ticagrelor (see section "Warnings and Precautions"))
    - anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
    - dronedarone, a medicine to treat abnormal heart beat
    - some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)).

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

- If you are taking**:**
    - some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
    - St John's Wort (Hypericum perforatum), a herbal product used for depression
    - rifampicin, an antibiotic
      If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban Accord and if you should be kept under closer observation.

Pregnancy and breast-feeding
Do not take Rivaroxaban Accord if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban Accord. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

Driving and using machines

Rivaroxaban Accord may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

Rivaroxaban Accord contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Rivaroxaban Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is one 2.5 mg tablet twice a day. Take Rivaroxaban Accord around the same time every day (for example, one tablet in the morning and one in the evening). This medicine can be taken with or without food.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban Accord. The tablet may be crushed and mixed with water or apple puree immediately before you take it.
If necessary, your doctor may also give you the crushed Rivaroxaban Accord tablet through a stomach tube.

Rivaroxaban Accord will not be given to you on its own.
Your doctor will also tell you to take acetylsalicylic acid.
If you get Rivaroxaban Accord after an acute coronary syndrome, your doctor may tell you to also take ticlopidine.
If you get Rivaroxaban Accord after a procedure to open a narrowed or closed artery of your leg to restore blood flow, your doctor may also prescribe clopidogrel for you to take in addition to acetylsalicylic acid for a short while.

Your doctor will tell you how much of these to take (usually between 75 to 100 mg acetylsalicylic acid daily or a daily dose of 75 to 100 mg acetylsalicylic acid plus a daily dose of either 75 mg clopidogrel or a standard daily dose of ticlopidine).

When to start Rivaroxaban Accord
Treatment with Rivaroxaban Accord after an acute coronary syndrome should be started as soon as possible after stabilisation of the acute coronary syndrome, at the earliest 24 hours after admission to hospital and at the time when parenteral (via injection) anticoagulation therapy would normally be stopped.
Your doctor will tell you when to start treatment with Rivaroxaban Accord if you have been diagnosed with coronary artery disease or peripheral artery disease.
Your doctor will decide how long you must continue treatment.

If you take more Rivaroxaban Accord than you should
Contact your doctor immediately if you have taken too many Rivaroxaban Accord tablets. Taking too much Rivaroxaban Accord increases the risk of bleeding.

If you forget to take Rivaroxaban Accord

Do not take a double dose to make up for a missed dose. If you miss a dose, take your next dose at the usual time.

If you stop taking Rivaroxaban Accord
Take Rivaroxaban Accord on a regular basis and for as long as your doctor keeps prescribing it.

Do not stop taking Rivaroxaban Accord without talking to your doctor first. If you stop taking this medicine, it may increase your risk of having another heart attack or stroke or dying from a disease related to your heart or your blood vessels.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Rivaroxaban Accord may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

Tell your doctor immediately if you experience any of the following side effects:
- **Signs of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
  - long or excessive bleeding
  - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you under closer observation or change the treatment.

- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

  The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Signs of severe allergic reactions**
  - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

  The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

Overall list of possible side effects

Common (may affect up to 1 in 10 people)
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood

- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- blood tests may show an increase in some liver enzymes

Uncommon (may affect up to 1 in 100 people)
- bleeding into the brain or inside the skull (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

Rare (may affect up to 1 in 1,000 people)
- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

Very rare (may affect up to 1 in 10,000 people)
- accumulation of eosinophils, a type of white granulocytic blood cells that cause inflammation in the lung (eosinophilic pneumonia)

Not known (frequency cannot be estimated from the available data)
- kidney failure after a severe bleeding
- bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy)
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivaroxaban Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on both the carton and on each blister or bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Crushed tablets
Crushed tablets are stable in water or apple puree for up tp 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rivaroxaban Accord contains

- The active substance is rivaroxaban. Each tablet contains 2.5 mg of rivaroxaban.
- The other ingredients are:

Tablet core
Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating
Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide yellow (E172)

What Rivaroxaban Accord looks like and contents of the pack

Rivaroxaban Accord 2.5 mg film-coated tablets are light yellow coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with “IL4” on one side and plain on other side.

Rivaroxaban Accord film-coated tablets are packed in clear PVC/Aluminium blisters available in:

- blister of 28, 56, 98, 100, 168 or 196 tablets, or
- perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.

Rivaroxaban Accord film-coated tablets are also available in HDPE bottles containing 30, 90 or 500 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Pharmadox Healthcare Limited
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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Rivaroxaban Accord 10 mg film-coated tablets
rivaroxaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivaroxaban Accord is and what it is used for

Rivaroxaban Accord contains the active substance rivaroxaban and is used in adults to
- prevent blood clots in the veins after a hip or knee replacement operation. Your doctor has prescribed this medicine for you because after an operation you are at an increased risk of getting blood clots.
- treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Rivaroxaban Accord belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

2. What you need to know before you take Rivaroxaban Accord

Do not take Rivaroxaban Accord
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

Do not take **Rivaroxaban Accord** and tell your doctor if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before taking Rivaroxaban Accord.

Take special care with Rivaroxaban Accord

- if you have an increased risk of bleeding, as could be the case in situations such as:
  - moderate or severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section 'Other medicines and Rivaroxaban Accord')
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet), e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If any of the above apply to you, tell your doctor before you take Rivaroxaban Accord. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If you need to have an operation

- it is very important to take Rivaroxaban Accord before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Rivaroxaban Accord exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

Children and adolescents

Rivaroxaban Accord is not recommended for people under 18 years of age. There is not enough information on its use in children and adolescents.

Other medicines and Rivaroxaban Accord

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

If you are taking

- some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
- ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
- some medicines for bacterial infections (e.g. clarithromycin, erythromycin)

- some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
- other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
- anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
- dronedarone, a medicine to treat abnormal heart beat
- some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)).

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

If you are taking**:**
- some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
- St John's Wort (Hypericum perforatum), a herbal product used for depression
- rifampicin, an antibiotic

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban Accord and if you should be kept under closer observation.

Pregnancy and breast-feeding
Do not take Rivaroxaban Accord if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban Accord. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

Driving and using machines
Rivaroxaban Accord may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

Rivaroxaban Accord contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Rivaroxaban Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- To prevent blood clots in the veins after a hip or knee replacement operation
  The recommended dose is one tablet Rivaroxaban Accord 10 mg once a day.

- To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs, and for preventing blood clots from re-occurring

After at least 6 months blood clot treatment, the recommended dose is either one 10 mg tablet once a day or one 20 mg tablet once a day. Your doctor has prescribed you Rivaroxaban Accord 10 mg once a day.

Swallow the tablet preferably with water.
Take Rivaroxaban Accord can be taken with or without food.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban Accord. The tablet may be crushed and mixed with water or apple puree immediately before you take it.
If necessary, your doctor may also give you the crushed Rivaroxaban Accord tablet through a stomach tube.

When to take Rivaroxaban Accord
Take the tablet every day until your doctor tells you to stop.
Try to take the tablet at the same time every day to help you to remember it.
Your doctor will decide how long you must continue treatment.

To prevent blood clots in the veins after a hip or knee replacement operation:
Take the first tablet 6-10 hours after your operation.
If you have had a major hip operation you will usually take the tablets for 5 weeks.
If you have had a major knee operation you will usually take the tablets for 2 weeks.

If you take more Rivaroxaban Accord than you should
Contact your doctor immediately if you have taken too many Rivaroxaban Accord tablets. Taking too much Rivaroxaban Accord increases the risk of bleeding.

If you forget to take Rivaroxaban Accord
If you have missed a dose, take it as soon as you remember. Take the next tablet on the following day and then carry on taking a tablet once a day as normal.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Rivaroxaban Accord
Do not stop taking Rivaroxaban Accord without talking to your doctor first, because Rivaroxaban Accord prevents the development of a serious condition.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Rivaroxaban Accord may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

Tell your doctor immediately if you experience any of the following side effects:
- **Sign of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
  - long or excessive bleeding

- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you under closer observation or change the treatment.

- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

  The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Sign of severe allergic reactions**
  - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

  The frequencies of severe allergic reactions are very rare anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

Overall list of possible side effects

Common (may affect up to 1 in 10 people)
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- blood tests may show an increase in some liver enzymes

Uncommon (may affect up to 1 in 100 people)
- bleeding into the brain or inside the skull (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

Rare (may affect up to 1 in 1,000 people)
- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

Very rare (may affect up to 1 in 10,000 people)
- accumulation of eosinophils, a type of white granulocytic blood cells that cause inflammation in the lung (eosinophilic pneumonia)

Not known (frequency cannot be estimated from the available data)
- kidney failure after a severe bleeding
- bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy)
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivaroxaban Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister or bottle after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Crushed tablets
Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rivaroxaban Accord contains
- The active substance is rivaroxaban. Each tablet contains 10 mg of rivaroxaban.
- The other ingredients are:

Tablet core
Lactose monohydrate
Croscarmellose sodium (E468)

Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating
Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

What Rivaroxaban Accord looks like and contents of the pack

Rivaroxaban Accord 10 mg film-coated tablets are light pink to pink coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with "IL1" on one side and plain on other side.

Rivaroxaban Accord film-coated tablets are packed in clear PVC/Aluminium blisters available in:
- blister of 5, 10, 14, 28, 30, 98 or 100 tablets, or
- perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.

Rivaroxaban Accord film-coated tablets are also available in HDPE bottles containing 30, 90 or 500 tablets.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Rivaroxaban Accord 15 mg film-coated tablets
Rivaroxaban Accord 20 mg film-coated tablets
rivaroxaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivaroxaban Accord is and what it is used for

Rivaroxaban Accord contains the active substance rivaroxaban and is used in adults to:
- prevent blood clots in brain (stroke) and other blood vessels in your body if you have a form of irregular heart rhythm called non-valvular atrial fibrillation.
- treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Rivaroxaban Accord is used in children and adolescents below 18 years and with a body weight of 30 kg or more to:
- treat blood clots and prevent re-occurrence of blood clots in the veins or in the blood vessels of the lungs, following initial treatment of at least 5 days with injectable medicines used to treat blood clots.

Rivaroxaban Accord belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

2. What you need to know before you take Rivaroxaban Accord

Do not take Rivaroxaban Accord
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open

- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast feeding

Do not take **Rivaroxaban Accord and tell your doctor** if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before taking Rivaroxaban Accord.

Take special care with Rivaroxaban Accord
- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease for adults, and moderate or severe kidney disease for children and adolescents, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section 'Other medicines and Rivaroxaban Accord')
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet) e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If any of the above apply to you, tell your doctor before you take Rivaroxaban Accord. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If you need to have an operation
- it is very important to take Rivaroxaban Accord before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Rivaroxaban Accord before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

Children and adolescents
Rivaroxaban Accord is **not recommended for children with a body weight below 30 kg**. There is not enough information on the use of Rivaroxaban Accord in children and adolescents in the adult indications.

Other medicines and Rivaroxaban Accord

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

If you are taking
- some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin
- ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
- some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
- some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
- other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
- anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
- dronedarone, a medicine to treat abnormal heart beat
- some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)).

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

If you are taking
- some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
- St John's Wort (Hypericum perforatum), a herbal product used for depression
- rifampicin, an antibiotic

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban Accord and if you should be kept under closer observation.

Pregnancy and breast-feeding
Do not take Rivaroxaban Accord if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban Accord. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

Driving and using machines
Rivaroxaban Accord may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

Rivaroxaban Accord contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Rivaroxaban Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You must take Rivaroxaban Accord together with a meal.
Swallow the tablet(s) preferably with water.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban Accord. The tablet may be crushed and mixed with water or apple puree immediately before you take it. This mixture should be immediately followed by food.
If necessary, your doctor may also give you the crushed Rivaroxaban Accord tablet through a stomach tube.

How much to take

- **Adults**
  - To prevent blood clots in brain (stroke) and other blood vessels in your body
    The recommended dose is one tablet Rivaroxaban Accord 20 mg once a day.
    If you have kidney problems, the dose may be reduced to one tablet Rivaroxaban Accord 15 mg once a day.

    If you need a procedure to treat blocked blood vessels in your heart (called a percutaneous coronary intervention - PCI with an insertion of a stent), there is limited evidence to reduce the dose to one tablet Rivaroxaban Accord 15 mg once a day (or to one tablet Rivaroxaban Accord 10 mg once a day in case your kidneys are not working properly) in addition to an antiplatelet medicinal product such as clopidogrel.

  - To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs, and for preventing blood clots from re-occurring.
    The recommended dose is one tablet Rivaroxaban Accord 15 mg twice a day for the first 3 weeks. For treatment after 3 weeks, the recommended dose is one tablet Rivaroxaban Accord 20 mg once a day.
    After at least 6 months blood clot treatment your doctor may decide to continue treatment with either one 10 mg tablet once a day or one 20 mg tablet once a day.
    If you have kidney problems and take one tablet Rivaroxaban Accord 20 mg once a day, your doctor may decide to reduce the dose for the treatment after 3 weeks to one tablet Rivaroxaban Accord 15 mg once a day if the risk for bleeding is greater than the risk for having another blood clot.

- **Children and adolescents**
  The dose of Rivaroxaban Accord depends on the body weight, and will be calculated by the doctor.
  - The recommended dose for children and adolescents with a **body weight between 30 kg and less than 50 kg** is one **Rivaroxaban Accord 15 mg tablet** once a day.
  - The recommended dose for children and adolescents with a **body weight of 50 kg or more** is one **Rivaroxaban Accord 20 mg tablet** once a day.

Take each Rivaroxaban Accord dose with a drink (e.g. water or juice) during a meal. Take the tablets every day at approximately the same time. Consider setting an alarm to remind you.
For parents or caregivers: please observe the child to ensure the full dose is taken.

As the Rivaroxaban Accord dose is based on body weight it is important to keep scheduled doctor's visits because the dose may need to be adjusted as the weight changes.
Never adjust the dose of Rivaroxaban Accord by yourself. The doctor will adjust the dose if necessary.

Do not split the tablet in an attempt to provide a fraction of a tablet dose. If a lower dose is required please use the alternative presentation of rivaroxaban granules for oral suspension available on the market.
For children and adolescents who are unable to swallow tablets whole, please use rivaroxaban granules for oral suspension.

If the oral suspension is not available, you may crush the Rivaroxaban Accord tablet and mix with water or apple puree immediately before taking. Take some food after taking this mixture. If necessary, your doctor may also give the crushed Rivaroxaban Accord tablet through a stomach tube.

If you spit up the dose or vomit
- less than 30 minutes after you have taken Rivaroxaban Accord, take a new dose.
- more than 30 minutes after you have taken Rivaroxaban Accord, do not take a new dose. In this case, take the next Rivaroxaban Accord dose at the usual time.

Contact the doctor if you repeatedly spit up the dose or vomit after taking Rivaroxaban Accord.

When to take Rivaroxaban Accord
Take the tablet(s) every day until your doctor tells you to stop.
Try to take the tablet(s) at the same time every day to help you to remember it.
Your doctor will decide how long you must continue treatment.

To prevent blood clots in the brain (stroke) and other blood vessels in your body:
If your heart beat needs to be restored to normal by a procedure called cardioversion, take Rivaroxaban Accord at the times your doctor tells you.

If you take more Rivaroxaban Accord than you should

Contact your doctor immediately if you have taken too many Rivaroxaban Accord tablets. Taking too much Rivaroxaban Accord increases the risk of bleeding.

If you forget to take Rivaroxaban Accord
- Adults, children and adolescents:
  If you are taking one 20 mg tablet or one 15 mg tablet once a day and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.
- Adults:
  If you are taking one 15 mg tablet twice a day and have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets in a single day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.

If you stop taking Rivaroxaban Accord
Do not stop taking Rivaroxaban Accord without talking to your doctor first, because Rivaroxaban Accord treats and prevents serious conditions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Rivaroxaban Accord may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

Tell your doctor immediately if you or your child experience any of the following side effects:

- **Sign of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)
  - long or excessive bleeding
  - exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you under closer observation or change the treatment.

Signs of severe skin reactions

- spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
- a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to 1 in 10,000 people).

Signs of severe allergic reactions

- swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

Overall list of possible side effects found in adults, children and adolescents

Common (may affect up to 1 in 10 people)

- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- blood tests may show an increase in some liver enzymes

Uncommon (may affect up to 1 in 100 people)

- bleeding into the brain or inside the skull (see above, signs of bleeding)

- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth
- hives

Rare (may affect up to 1 in 1,000 people):
- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

Very rare (may affect up to 1 in 10,000 people)
- accumulation of eosinophils, a type of white granulocytic blood cells that cause inflammation in the lung (eosinophilic pneumonia)

Not known (frequency cannot be estimated from the available data)
- kidney failure after a severe bleeding
- bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy)
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

Side effects in children and adolescents
In general, the side effects observed in children and adolescents treated with Rivaroxaban Accord were similar in type to those observed in adults and were primarily mild to moderate in severity.

Side effects that were observed more often in children and adolescents:

Very common (may affect more than 1 in 10 people)
- headache
- fever
- nose bleeding
- vomiting

Common (may affect up to 1 in 10 people)
- raised heartbeat
- blood tests may show an increase in bilirubin (bile pigment)
- thrombocytopenia (low number of platelets which are cells that help blood to clot)
- heavy menstrual bleeding

Uncommon (may affect up to 1 in 100 people)
- blood tests may show an increase in a subcategory of bilirubin (direct bilirubin, bile pigment)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivaroxaban Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and on each blister or bottle after EXP.
The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Crushed tablets
Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rivaroxaban Accord contains
- The active substance is rivaroxaban. Each tablet contains 15 mg or 20 mg of rivaroxaban.
- The other ingredients are:

Tablet core
Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating
Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

What Rivaroxaban Accord looks like and contents of the pack

Rivaroxaban Accord 15 mg: Red coloured, round, biconvex, approximately 5.00 mm in diameter, film coated tablets debossed with ‘‘IL’’ on one side and ‘‘2’’ on other side.

Rivaroxaban Accord 15 mg film-coated tablets are packed in clear PVC/Aluminium blisters available in:
- blister of 10, 14, 28, 30, 42, 48, 56, 90, 98 or 100 tablets, or
- perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.

Rivaroxaban Accord 15 mg film-coated tablets are also available in HDPE bottles containing 30, 90 or 500 tablets.

Rivaroxaban Accord 20 mg: Dark red coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with ‘‘IL3’’ on one side and plain on other side.

Rivaroxaban Accord 20 mg film-coated tablets are packed in clear PVC/Aluminium blisters available in:

- blister of 10, 14, 28, 30, 42, 56, 90, 98 or 100 tablets or
- perforated unit dose blisters of 10 x 1 or 100 x 1 tablets.

Rivaroxaban Accord 20 mg film-coated tablets are also available in HDPE bottles containing 30, 90 or 500 tablets.

Not all pack sizes may be marketed.

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Package leaflet: Information for the user

Rivaroxaban Accord 15 mg film-coated tablets
Rivaroxaban Accord 20 mg film-coated tablets

Treatment Initiation Pack
Not for use in children.
rivaroxaban

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivaroxaban Accord is and what it is used for

Rivaroxaban Accord contains the active substance rivaroxaban and is used in adults to:
- treat blood clots in the veins of your legs (deep vein thrombosis) and in the blood vessels of your lungs (pulmonary embolism), and to prevent blood clots from re-occurring in the blood vessels of your legs and/or lungs.

Rivaroxaban Accord belongs to a group of medicines called antithrombotic agents. It works by blocking a blood clotting factor (factor Xa) and thus reducing the tendency of the blood to form clots.

2. What you need to know before you take Rivaroxaban Accord

Do not take Rivaroxaban Accord
- if you are allergic to rivaroxaban or any of the other ingredients of this medicine (listed in section 6)
- if you are bleeding excessively
- if you have a disease or condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes)
- if you are taking medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), except when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open
- if you have a liver disease which leads to an increased risk of bleeding
- if you are pregnant or breast-feeding

Do not take **Rivaroxaban Accord** and tell your doctor if any of these apply to you.

Warnings and precautions
Talk to your doctor or pharmacist before taking Rivaroxaban Accord.

Take special care with Rivaroxaban Accord
- if you have an increased risk of bleeding, as could be the case in situations such as:
  - severe kidney disease, since your kidney function may affect the amount of medicine that works in your body
  - if you are taking other medicines to prevent blood clotting (e.g. warfarin, dabigatran, apixaban or heparin), when changing anticoagulant treatment or while getting heparin through a venous or arterial line to keep it open (see section 'Other medicines and Rivaroxaban Accord')
  - bleeding disorders
  - very high blood pressure, not controlled by medical treatment
  - diseases of your stomach or bowel that might result in bleeding, e.g. inflammation of the bowels or stomach, or inflammation of the oesophagus (gullet), e.g. due to gastroesophageal reflux disease (disease where stomach acid goes upwards into the oesophagus) or tumours located in the stomach or bowels or genital tract or urinary tract
  - a problem with the blood vessels in the back of your eyes (retinopathy)
  - a lung disease where your bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from your lung
- if you have a prosthetic heart valve
- if your doctor determines that your blood pressure is unstable or another treatment or surgical procedure to remove the blood clot from your lungs is planned.
- if you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor who will decide if the treatment may need to be changed.

If any of the above apply to you, tell your doctor before you take Rivaroxaban Accord. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.

If you need to have an operation:
- it is very important to take Rivaroxaban Accord before and after the operation exactly at the times you have been told by your doctor.
- If your operation involves a catheter or injection into your spinal column (e.g. for epidural or spinal anaesthesia or pain reduction):
  - it is very important to take Rivaroxaban Accord before and after the injection or removal of the catheter exactly at the times you have been told by your doctor
  - tell your doctor immediately if you get numbness or weakness of your legs or problems with your bowel or bladder after the end of anaesthesia, because urgent care is necessary.

Children and adolescents
Rivaroxaban Accord treatment initiation pack is not recommended for people under 18 years of age as it is specifically designed for initiation of treatment in adult patients and is not appropriate for use in children and adolescents.

Other medicines and Rivaroxaban Accord
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.
If you are taking
- some medicines for fungal infections (e.g. fluconazole, itraconazole, voriconazole, posaconazole), unless they are only applied to the skin

- ketoconazole tablets (used to treat Cushing's syndrome - when the body produces an excess of cortisol)
- some medicines for bacterial infections (e.g. clarithromycin, erythromycin)
- some anti-viral medicines for HIV / AIDS (e.g. ritonavir)
- other medicines to reduce blood clotting (e.g. enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol)
- anti-inflammatory and pain relieving medicines (e.g. naproxen or acetylsalicylic acid)
- dronedarone, a medicine to treat abnormal heart beat
- some medicines to treat depression (selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)).

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be increased. Your doctor will decide, if you should be treated with this medicine and if you should be kept under closer observation.
If your doctor thinks that you are at increased risk of developing stomach or bowel ulcers, he may also use a preventative ulcer treatment.

If you are taking**:**
- some medicines for treatment of epilepsy (phenytoin, carbamazepine, phenobarbital)
- St John's Wort (Hypericum perforatum), a herbal product used for depression
- rifampicin, an antibiotic

If any of the above apply to you, tell your doctor before taking Rivaroxaban Accord, because the effect of Rivaroxaban Accord may be reduced. Your doctor will decide, if you should be treated with Rivaroxaban Accord and if you should be kept under closer observation.

Pregnancy and breast-feeding
Do not take Rivaroxaban Accord if you are pregnant or breast feeding. If there is a chance that you could become pregnant, use a reliable contraceptive while you are taking Rivaroxaban Accord. If you become pregnant while you are taking this medicine, tell your doctor immediately, who will decide how you should be treated.

Driving and using machines
Rivaroxaban Accord may cause dizziness (common side effect) or fainting (uncommon side effect) (see section 4, 'Possible side effects'). You should not drive, ride a bicycle or use any tools or machines if you are affected by these symptoms.

Rivaroxaban Accord contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially "sodium-free".

3. How to take Rivaroxaban Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You must take Rivaroxaban Accord together with a meal.
Swallow the tablet(s) preferably with water.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Rivaroxaban Accord. The tablet may be crushed and mixed with water or apple puree immediately before you take it. This mixture should be immediately followed by food.
If necessary, your doctor may also give you the crushed Rivaroxaban Accord tablet through a stomach tube.

How much to take
The recommended dose is one tablet Rivaroxaban Accord 15 mg twice a day for the first 3 weeks. For treatment after 3 weeks, the recommended dose is one tablet Rivaroxaban Accord 20 mg once a day.
This Rivaroxaban Accord 15 mg and 20 mg treatment initiation pack is only for the first 4 weeks of treatment. Upon completion of this pack, treatment will continue on Rivaroxaban Accord 20 mg once daily as your doctor has told you.
If you have kidney problems, your doctor may decide to reduce the dose for the treatment after 3 weeks to one tablet Rivaroxaban Accord 15 mg once a day if the risk for bleeding is greater than the risk for having another blood clot.

When to take Rivaroxaban Accord
Take the tablet(s) every day until your doctor tells you to stop.
Try to take the tablet(s) at the same time every day to help you to remember it.
Your doctor will decide how long you must continue treatment.

If you take more Rivaroxaban Accord than you should
Contact your doctor immediately if you have taken too many Rivaroxaban Accord tablets. Taking too much Rivaroxaban Accord increases the risk of bleeding.

If you forget to take Rivaroxaban Accord
- If you are taking one 15 mg tablet twice a day and have missed a dose, take it as soon as you remember. Do not take more than two 15 mg tablets in a single day. If you forget to take a dose you can take two 15 mg tablets at the same time to get a total of two tablets (30 mg) on one day. On the following day you should carry on taking one 15 mg tablet twice a day.
- If you are taking one 20 mg tablet once a day and have missed a dose, take it as soon as you remember. Do not take more than one tablet in a single day to make up for a forgotten dose. Take the next tablet on the following day and then carry on taking one tablet once a day.

If you stop taking Rivaroxaban Accord
Do not stop taking Rivaroxaban Accord without talking to your doctor first, because Rivaroxaban Accord treats and prevents serious conditions.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Like other similar medicines to reduce the formation of blood clots, Rivaroxaban Accord may cause bleeding which may potentially be life threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases the bleeding may not be obvious.

Tell your doctor immediately if you experience any of the following side effects:
- **Signs of bleeding**
  - bleeding into the brain or inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizures, decreased level of consciousness, and neck stiffness. A serious medical emergency. Seek medical attention immediately!)

- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris

Your doctor may decide to keep you under closer observation or change the treatment.

- **Signs of severe skin reactions**
  - spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
  - a drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to 1 in 10,000 people).

- **Signs of severe allergic reactions**
  - swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to 1 in 10,000 people) and uncommon (angioedema and allergic oedema; may affect up to 1 in 100 people).

Overall list of possible side effects

Common (may affect up to 1 in 10 people):
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleed, bleeding in the gum
- bleeding into the eye (including bleeding from the whites of the eyes)
- bleeding into tissue or a cavity of the body (haematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- oozing of blood or fluid from surgical wound
- swelling in the limbs
- pain in the limbs
- impaired function of the kidneys (may be seen in tests performed by your doctor)
- fever
- stomach ache, indigestion, feeling or being sick, constipation, diarrhoea
- low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- blood tests may show an increase in some liver enzymes

Uncommon (may affect up to 1 in 100 people)
- bleeding into the brain or inside the skull (see above, signs of bleeding)
- bleeding into a joint causing pain and swelling
- thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (may be seen in tests performed by your doctor)
- blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- feeling unwell
- faster heartbeat
- dry mouth

- hives

Rare (may affect up to 1 in 1,000 people)
- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis incl. hepatocellular injury (inflamed liver incl. liver injury)
- yellowing of the skin and eye (jaundice)
- localised swelling
- collection of blood (haematoma) in the groin as a complication of the cardiac procedure where a catheter is inserted in your leg artery (pseudoaneurysm)

Very rare (may affect up to 1 in 10,000 people)
- accumulation of eosinophils, a type of white granulocytic blood cells that cause inflammation in the lung (eosinophilic pneumonia)

Not known (frequency cannot be estimated from the available data)
- kidney failure after a severe bleeding
- bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy)
- increased pressure within muscles of the legs or arms after a bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after a bleeding)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivaroxaban Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Crushed tablets
Crushed tablets are stable in water or apple puree for up to 4 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Contents of the pack and other information

What Rivaroxaban Accord contains
- The active substance is rivaroxaban. Each tablet contains 15 mg or 20 mg of rivaroxaban respectively.
- The other ingredients are:

Tablet core

Lactose monohydrate
Croscarmellose sodium (E468)
Sodium laurilsulfate (E487)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Cellulose, microcrystalline (E460)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating
Macrogol 4000 (E1521)
Hypromellose 2910 (nominal viscosity 5.1 mPa.S) (E464)
Titanium dioxide (E171)
Iron oxide red (E172)

What Rivaroxaban Accord looks like and contents of the pack

Rivaroxaban Accord 15 mg: Red coloured, round, biconvex, approximately 5.00 mm in diameter, film coated tablets debossed with ‘‘IL’’ on one side and ‘‘2’’ on other side.
Rivaroxaban Accord 20 mg: Dark red coloured, round, biconvex, approximately 6.00 mm in diameter, film coated tablets debossed with ‘‘IL3’’ on one side and plain on other side.
First 4 weeks treatment initiation pack: each pack of 49 film-coated tablets for the first 4 weeks of treatment contains: 42 film-coated tablets of 15 mg rivaroxaban and 7 film-coated tablets of 20 mg rivaroxaban in a wallet.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.