Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rivaroxaban Clonmel 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 58 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, round, biconvex film-coated tablets with a diameter of approximately 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Converting from Rivaroxaban Clonmel to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Rivaroxaban Clonmel to VKA.
Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban Clonmel can contribute to an elevated INR.
In patients converting from Rivaroxaban Clonmel 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 Clonmel and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban Clonmel. Once Rivaroxaban Clonmel 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 Clonmel
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban Clonmel 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 Clonmel to parenteral anticoagulants
Give the first dose of parenteral anticoagulant at the time the next Rivaroxaban Clonmel 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 Clonmel 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 Clonmel 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 2.5 mg tablets in children aged 0 to 18 years have not been established. No data are available. Therefore, Rivaroxaban Clonmel 2.5 mg tablets are not recommended for use in children below 18 years of age.

Method of administration
Rivaroxaban Clonmel 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 Clonmel 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 are to be carefully observed for signs of bleeding.
It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rivaroxaban administration should be discontinued if severe haemorrhage occurs (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 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 Clonmel is to be used with caution (see section 4.5).

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

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 within 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.

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 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 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.

Excipients

Rivaroxaban Clonmel 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 nonmajor 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 Clonmel 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 Clonmel 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	7,750	20 mg	41 months

non-valvular atrial fibrillation			
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 VTE in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of VTE 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 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]		
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
HPRA Pharmacovigilance
Website: www.hpra.ie

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 anti-platelets therapy 98.8% received clopidogrel, 0.9% received ticlopidine and 0.3 % received prasugrel. Patients received the first dose of rivaroxaban at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.

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

Relative to placebo, rivaroxaban significantly reduced the primary composite endpoint of CV death, MI or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 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 %)
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=3,114 n (%) HR (95% CI) p-value [b]**	**Placebo N=3,096 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 %)

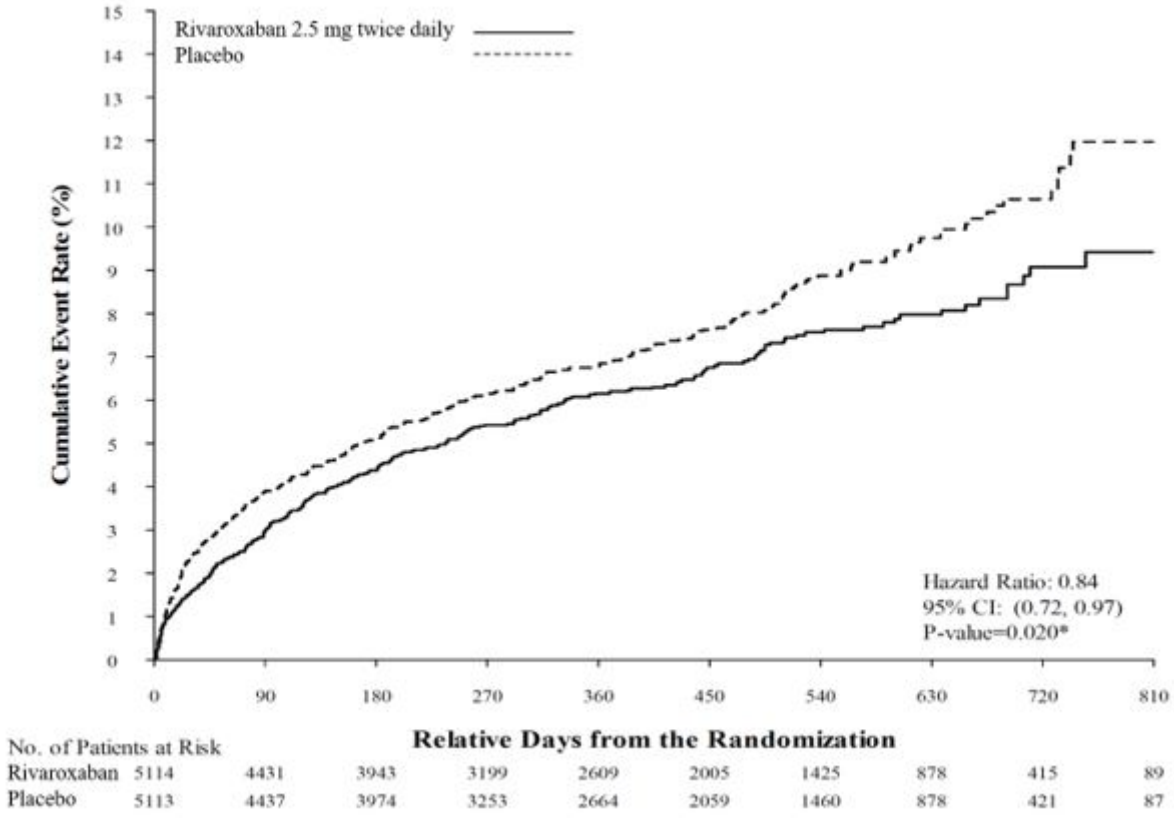
[a] modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
[b] vs placebo; Log-Rank p-value
** nominally significant

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 revascularisation or asymptomatic carotid artery stenosis ≥ 50 %.

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

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

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

For the primary efficacy outcome, the observed benefit of rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily compared with ASA 100 mg once daily was HR=0.89 (95 % CI 0.7-1.1) in patients ≥ 75 years (incidence: 6.3 % vs 7.0 %) and HR=0.70 (95 % CI 0.6-0.8) in patients < 75 years (3.6 % vs 5.0 %). For modified ISTH major bleeding, the observed risk increase was HR=2.12 (95 % CI 1.5-3.0) in patients ≥ 75 years (5.2 % vs 2.5 %) and HR=1.53 (95 % CI 1.2-1.9) in patients < 75 years (2.6 % vs 1.7 %).

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

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=9,152**		**ASA 100 mg od N=9,126**			
	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

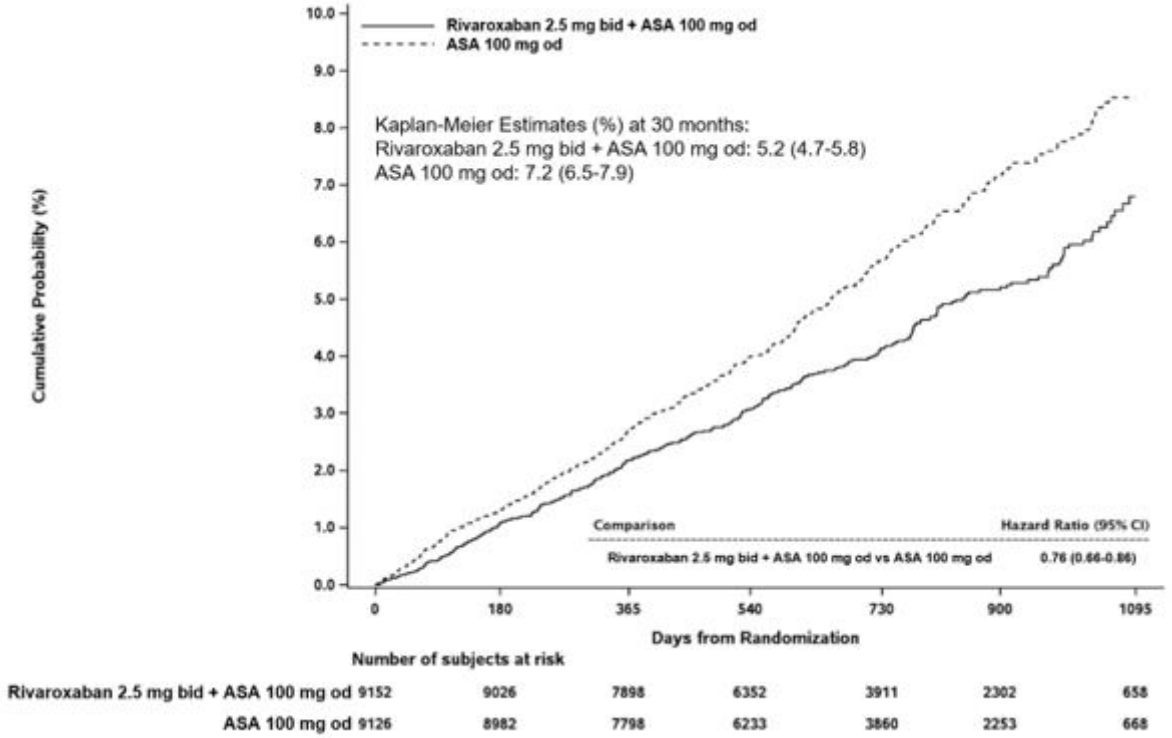
Table 8: Safety results from phase III COMPASS

Study population	**Patients with CAD/PAD** [a)]		
Treatment dose	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od N=9,152 n (Cum. risk %)**	**ASA 100 mg od N=9,126 n (Cum. risk %)**	**Hazard Ratio (95 % CI) p-value** [b)]
Modified ISTH major bleeding	**288 (3.9 %)**	**170 (2.5 %)**	**1.70 (1.40;2.05) p<0.00001**
- Fatal bleeding event	**15 (0.2 %)**	**10 (0.2 %)**	**1.49 (0.67;3.33) p=0.32164**
- Symptomatic bleeding in critical organ (non-fatal)	**63 (0.9 %)**	**49 (0.7 %)**	**1.28 (0.88;1.86) p=0.19679**
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	**10 (0.1 %)**	**8 (0.1 %)**	**1.24 (0.49;3.14) p=0.65119**
- Bleeding leading to hospitalisation (non-fatal, not in critical organ, not requiring reoperation)	**208 (2.9 %)**	**109 (1.6 %)**	**1.91 (1.51;2.41) p<0.00001**
- With overnight stay	**172 (2.3 %)**	**90 (1.3 %)**	**1.91 (1.48;2.46) p<0.00001**
- Without overnight stay	**36 (0.5 %)**	**21 (0.3 %)**	**1.70 (0.99;2.92) p=0.04983**
Major gastrointestinal bleeding	**140 (2.0 %)**	**65 (1.1 %)**	**2.15 (1.60;2.89) p<0.00001**

Major intracranial bleeding	**28 (0.4 %)**	**24 (0.3 %)**	**1.16 (0.67;2.00) p=0.59858**

[a] intention-to-treat analysis set, primary analyses
[b] vs ASA 100 mg; Log-Rank p-value
bid: twice daily; CI: confidence interval; Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months; ISTH: International Society on Thrombosis and Haemostasis; od: once daily

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 aetiology 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 haemostasis 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 aetiology 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 aetiology	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 aetiology

[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 ≥ 5 g/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 hospitalisation of decompensated heart failure (HF) which were randomly assigned into one of the two treatment groups: rivaroxaban 2.5 mg twice daily (N=2,507) or matching placebo (N=2,515), respectively. The overall median study treatment duration was 504 days.
Patients must have had symptomatic HF for at least 3 months and left ventricular ejection fraction (LVEF) of ≤ 40% within one year of enrolment. At baseline, the median ejection fraction was 34 % (IQR: 28 %-38 %) and 53 % of subjects were NYHA Class III or IV.

The primary efficacy analysis (i.e. composite of all-cause mortality, MI, or stroke) showed no statistically significant difference between the rivaroxaban 2.5 mg 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 multicentre study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies). The study was terminated prematurely after the enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were 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 V_{ss} being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the 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 post-natal 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
Cellulose, microcrystalline
Lactose monohydrate
Povidone
Starch, pregelatinised
Crospovidone
Sodium lauryl sulfate
Magnesium stearate

Film-coat
Hypromellose E464
Titanium dioxide E171
Macrogol 4000 E1521
Iron oxide yellow E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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

PVC/PVdC/Aluminium blisters

Packs of 10, 10x1, 14, 14x1, 15, 15x1, 20, 20x1, 28, 28x1, 30, 30x1, 42, 42x1, 56, 56x1, 60, 60x1, 98, 98x1, 100, 100x1, 168, 168x1, 196 and 196x1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special 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

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
E91 D768
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/035/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th January 2023

10 DATE OF REVISION OF THE TEXT

May 2025