To be sold by retail on the prescription of a Specialist only

ROVOR

1. Generic Name:

Rivaroxaban Tablets

2. Qualitative and quantitative composition:

Each film-coated tablet contains:

Rivaroxaban..... 2.5 mg

Excipients…….....q.s.

Colours: Yellow oxide of Iron and Titanium Dioxide I.P.

The other ingredients are:

Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Sodium Lauryl Sulphate, Hydroxypropylmethylcellulose, Magnesium Stearate, Opadry 03F520254 Yellow (Hypromellose, PolyEthylene glycol, Titanium Dioxide, Yellow Oxide of Iron).

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: Rivaroxaban 2.5 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Rivaroxaban 2.5 mg tablet, 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.

4.2 Posology and method of administration:

Posology

The recommended dose is 2.5 mg twice daily.

ACS

Patients taking Rivaroxaban 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.

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.

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.

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 is discontinued INR testing may be done reliably at least 24 hours after the last dose.

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 is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min.

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).

Hepatic impairment

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.

Elderly population

No dose adjustment.

The risk of bleeding increases with increasing age.

Body weight

No dose adjustment.

Gender

No dose adjustment.

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 is not recommended for use in children below 18 years of age.

Method of administration

Rivaroxaban is for oral use.

The tablets can be taken with or without food.

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

The crushed Rivaroxaban tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water.

4.3 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients.
- 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 or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA).
- Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use:

In ACS patients, efficacy and safety of Rivaroxaban 2.5 mg have been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine. 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.

Based on 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 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. 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.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

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

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) 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.

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.

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.

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.

Patients on treatment with Rivaroxaban and ASA or with Rivaroxaban and ASA plus clopidogrel/ticlopidine 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

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. 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.

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.

Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban 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 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.

Elderly population

Increasing age may increase haemorrhagic risk.

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. 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 contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Drug-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.

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.

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.

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.

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.

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.

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

Laboratory parameters

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

4.6 Use in special populations

Pregnancy

Safety and efficacy of Rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Rivaroxaban is contraindicated during pregnancy.

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. 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.

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. 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 reported thirteen phase III studies including 53,103 patients exposed to Rivaroxaban.

Number of patients studied, total daily dose and maximum treatment duration in 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 DVT, 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
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
* Patients exposed to at least one dose of rivaroxaban			

The most commonly reported adverse reactions in patients receiving Rivaroxaban were bleedings. The most commonly reported bleedings were epistaxis (4.5%) and gastrointestinal tract haemorrhage (3.8%).

Bleeding* and anaemia events rates in patients exposed to Rivaroxaban across the completed 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
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**
* For all Rivaroxaban studies all bleeding events are collected, reported and adjudicated. ** In the reported COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied		

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with Rivaroxaban are summarised in 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)

All adverse reactions reported in patients in phase III clinical trials or through post-marketing use*

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				
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
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. As incidence of adverse reactions did not increase and no new adverse reaction was identified, COMPASS study data were not included for frequency calculation in this table.				

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. Based on 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. 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 have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose:

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg Rivaroxaban or above.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of Rivaroxaban is available.

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 administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. 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 , or a specific procoagulant reversal 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.

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 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.

5.2 Pharmacodynamic properties:

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 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 twice daily ranged from 17 to 32 s and for 20 mg 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 20s.

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.

According to a reported 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.

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.

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. 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. 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. 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.

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.

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 (%)**	**Placebo N=5,113 n (%)**

	Hazard Ratio (HR) (95% CI) p-value [b)]	
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		

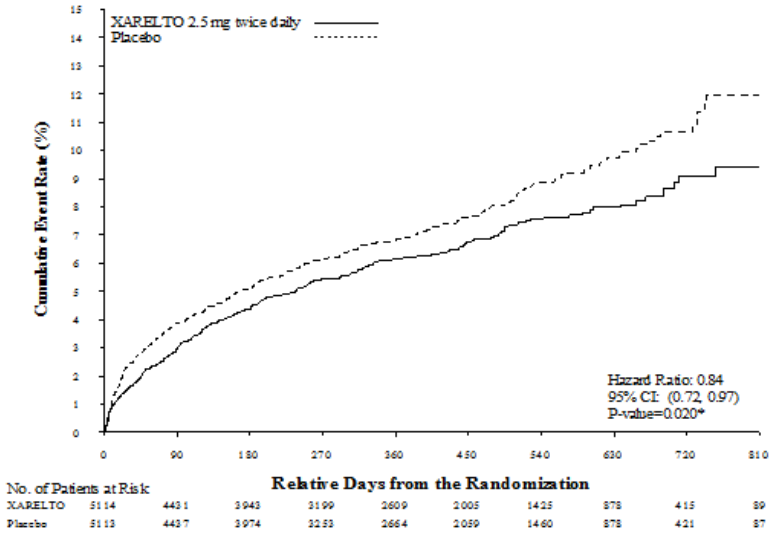
Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI

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		

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		

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



Patients with high risk triple positive antiphospholipid syndrome

In an investigator sponsored, randomized 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 randomized 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 randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). No events were reported in patients randomized 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 deferred the obligation to submit the results of studies with Rivaroxaban in one or more subsets of the paediatric population in the treatment of thromboembolic events. The European Medicines Agency has waived the obligation to submit the results of studies with Rivaroxaban in all subsets of the paediatric population in the prevention of thromboembolic events.

5.3 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.

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 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.

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.

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 for children and adolescents up to 18 years.

6. Nonclinical properties:

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

reported pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

7. Description:

Round, light yellow colored, biconvex film-coated tablets plain on both side.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

Available in blister pack of 10 tablets.

8.4 Storage and handing instructions:

- Store at a temperature not exceeding 30ºC, protected from light and moisture.
- Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

ROVOR

Rivaroxaban 2.5 mg tablets

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?

9.1. What ROVOR is and what it is used for

You have been given **ROVOR** 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.
ROVOR 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.
ROVOR 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.

ROVOR 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.

9.2. What you need to know before you take ROVOR

Do not take ROVOR

- if you are allergic to Rivaroxaban or any of the other ingredients of this medicine
- 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 ROVOR and tell your doctor if any of these apply to you**.**

Warnings and precautions

Talk to your doctor or pharmacist before taking ROVOR.
ROVOR 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 ROVOR

❖ 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
- 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)

- 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 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 ROVOR. 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 ROVOR 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 ROVOR 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

ROVOR 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 ROVOR

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 ROVOR, because the effect of ROVOR 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 ROVOR, because the effect of ROVOR may be reduced. Your doctor will decide, if you should be treated with ROVOR and if you should be kept under closer observation.

Pregnancy and breast-feeding

Do not take ROVOR 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 ROVOR. 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

ROVOR may cause dizziness (common side effect) or fainting (uncommon side effect). You should not drive or use machines if you are affected by these symptoms.

ROVOR 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".

9.3. How to take ROVOR

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 **ROVOR** 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 **ROVOR**. 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 **ROVOR** tablet through a stomach tube.

ROVOR will not be given to you on its own.

Your doctor will also tell you to take acetylsalicylic acid. If you get **ROVOR** after an acute coronary syndrome, your doctor may tell you to also take clopidogrel or ticlopidine.

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 ROVOR
Treatment with **ROVOR** 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 **ROVOR** 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 ROVOR than you should

Contact your doctor immediately if you have taken too many ROVOR tablets. Taking too much ROVOR increases the risk of bleeding.

If you forget to take ROVOR

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 ROVOR

Take **ROVOR** on a regular basis and for as long as your doctor keeps prescribing it.

Do not stop taking **ROVOR** 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.

9.4. Possible side effects

- Like all medicines, ROVOR can cause side effects, although not everybody gets them.
- Like other similar medicines (antithrombotic agents), ROVOR 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.

Possible side effects which may be a sign of bleeding

Tell your doctor immediately if you experience any of the following side effects:

- long or excessive bleeding
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris, which may be signs of bleeding.

Your doctor may decide to keep you under closer observation or change how you should be treated.

Possible side effects which may be a sign of severe skin reaction

Tell your doctor immediately if you experience skin reactions such as:

- spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Stevens Johnson syndrome/toxic epidermal necrolysis). The frequency of this side effect is very rare (up to 1 in 10,000).

- a drug reaction that causes rash, fever, inflammation of internal organs, hematologic abnormalities and systemic illness (DRESS syndrome). The frequency of this side effect is very rare (up to 1 in 10,000).

Possible side effects which may be a sign of severe allergic reactions

Tell your doctor immediately if you experience any of the following side effects:

- swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure. The frequencies of these side effects 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
- 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)

Not known (frequency cannot be estimated from the available data)

- kidney failure after a severe bleeding
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

9.5. How to store ROVOR

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. 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.

9.6. Contents of the pack and other information

What ROVOR contains

The active substance is Rivaroxaban. Each tablet contains 2.5 mg of Rivaroxaban.

The other ingredients are:

Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Sodium Lauryl Sulphate, Hydroxypropylmethylcellulose, Magnesium Stearate , Opadry 03F520254 Yellow (Hypromellose, PolyEthylene glycol, Titanium Dioxide, Yellow Oxide of Iron).

10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

32 No, Middle Camp, NH-10,

East District, Gangtok, Sikkim-737 135

11. Details of permission or licence number with date

M/563/2010 dated 03.09.2020

12. Date of revision

Not applicable

MARKETED BY

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IN/ROVOR 2.5 mg/OCT-20/01/PI