SUMMARY OF PRODUCT CHACTERISTICS

1. Name of the Medicinal Product

Rivaroxaban Film-Coated Tablets 15 mg /20 mg

2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Rivaroxaban…… 15mg /20mg

Excipient with known effect:

Each film-coated tablet contains lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Film-coated tablet

4. Clinical Particulars

4.1 Therapeutic indications

Adults

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population

For Rivaroxaban Tablet 15 mg

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

For Rivaroxaban Tablet 20 mg

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

4.2 Posology and method of administration

Posology

Prevention of stroke and systemic embolism in adults

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Rivaroxaban tablets 15/20 mg should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding.

If a dose is missed the patient should take Rivaroxaban tablets 15/20 mg immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults

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

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

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

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

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

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

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

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

Treatment of VTE and prevention of VTE recurrence in children and adolescents

Rivaroxaban tablets 15/20 mg treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment.

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

- Body weight of 50 kg or more:

a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.

- Body weight from 30 to 50 kg:

a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.

- For patients with body weight less 30 kg refer to the Summary of Product Characteristics of Rivaroxaban granules for oral suspension.

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

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

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day.

If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Rivaroxaban

- Prevention of stroke and systemic embolism:

VKA treatment should be stopped and Rivaroxaban tablets 15/20 mg therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.

- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence inpaediatric patients:

VKA treatment should be stopped and Rivaroxaban tablets 15/20 mg therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to Rivaroxaban tablets 15/20 mg, INR values will be falsely elevated after the intake of Rivaroxaban tablets 15/20 mg. The INR is not valid to measure the anticoagulant activity of Rivaroxaban tablets 15/20 mg, and therefore should not be used.

Converting from Rivaroxaban tablets 15/20 mg to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from Rivaroxaban tablets 15/20 mg to VKA. Continuous adequate anticoagulation should

be ensured during any transition to an alternate anticoagulant. It should be noted that Rivaroxaban tablets 15/20 mg can contribute to an elevated INR.

In patients converting from Rivaroxaban tablets 15/20 mg 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 tablets 15/20 mg and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaroxaban tablets 15/20 mg. Once Rivaroxaban tablets 15/20 mg is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Paediatric patients:

Children who convert from Rivaroxaban tablets 15/20 mg to VKA need to continue Rivaroxaban tablets 15/20 mg for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Rivaroxaban tablets 15/20 mg. Co-administration of Rivaroxaban tablets 15/20 mg and VKA is advised to continue until the INR is ≥ 2.0. Once Rivaroxaban tablets 15/20 mg is discontinued INR testing may be done reliably 24 hours after the last dose.

Converting from parenteral anticoagulants to Rivaroxaban tablets 15/20 mg

For adult and paediatric patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaroxaban tablets 15/20 mg 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 tablets 15/20 mg to parenteral anticoagulants

Discontinue Rivaroxaban tablets 15/20 mg and give the first dose of parenteral anticoagulant at the time the next Rivaroxaban tablets 15/20 mg dose would be taken.

Special populations

Renal impairment

Adults:

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Rivaroxaban tablets 15/20 mg is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min.

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

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily.
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modeling and has not been studied in this clinical setting.

When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

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

Paediatric population:

- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2): no dose adjustment is required, based on data in adults and limited data in paediatric patients.
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2):

Rivaroxaban tablets 15/20 mg is not recommended as no clinical data is available.

Hepatic impairment

Rivaroxaban tablets 15/20 mg is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

No clinical data is available in children with hepatic impairment.

Elderly population

No dose adjustment

Body weight

No dose adjustment for adults

For paediatric patients the dose is determined based on body weight.

Gender

No dose adjustment

Patients undergoing cardioversion

Rivaroxaban tablets 15/20 mg can be initiated or continued in patients who may require cardioversion.

For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaroxaban tablets 15/20 mg treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken Rivaroxaban tablets 15/20 mg as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement

There is limited experience of a reduced dose of 15 mg Rivaroxaban tablets 15/20 mg once daily (or 10 mg Rivaroxaban tablets 15/20 mg once daily for patients with moderate renal impairment [creatinine clearance 30 - 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement.

Paediatric population

The safety and efficacy of Rivaroxaban tablets 15/20 mg in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available.

Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Method of administration

Adults

Rivaroxaban tablets 15/20 mg are for oral use.

The tablets are to be taken with food.

Children and adolescents weighing 30 kg to 50 kg

Rivaroxaban tablets 15/20 mg is for oral use.

The patient should be advised to swallow the tablet with liquid. It should also be taken with food. The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be readministered and the next dose should be taken as scheduled. The tablet must not be split in an attempt to provide a fraction of a tablet dose.

Children and adolescents weighing more than 50 kg

Rivaroxaban tablets 15/20 mg is for oral use.

The patient should be advised to swallow the tablet with liquid. It should also be taken with food. The tablets should be taken approximately 24 hours apart.

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

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

Crushing of tablets

For patients who are unable to swallow whole tablets, Rivaroxaban granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.

The crushed tablet may be given through a nasogastric or gastric feeding tube.

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.

Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use

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

<u>Haemorrhagic risk</u>

As with other anticoagulants, patients taking Rivaroxaban tablets 15/20 mg 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 tablets 15/20 mg administration should be discontinued if severe haemorrhage occurs.

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

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

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.

Paediatric population

There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection.

The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Rivaroxaban tablets 15/20 mg 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.

Rivaroxaban tablets 15/20 mg should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.
Rivaroxaban tablets 15/20 mg is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2), as no clinical data is available.

Interaction with other medicinal products

The use of Rivaroxaban tablets 15/20 mg is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk.
No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4
and P-gp.
Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as nonsteroidal 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.

Other haemorrhagic risk factors

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

• bronchiectasis or history of pulmonary bleeding

Patients with cancer

Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.

In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated.

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 tablets 15/20 mg have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rivaroxaban tablets 15/20 mg provides adequate anticoagulation in this patient population. Treatment with Rivaroxaban tablets 15/20 mg 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 non-valvular atrial fibrillation who undergo PCI with stent placement

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

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

Rivaroxaban tablets 15/20 mg is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Rivaroxaban tablets 15/20 mg have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 20 mg rivaroxaban in these situations. To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban. Following

removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

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

No data is available on the timing of the placement or removal of neuraxial catheter in children while on Rivaroxaban tablets 15/20 mg. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban tablets 20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Rivaroxaban tablets 15/20 mg 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 tablets 15/20 mg contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

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

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rivaroxaban tablets 15/20 mg 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 Cmax. 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 Cmax. 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 Cmax 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 Cmax 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 Cmax. 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 coadministered 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 Ctrough of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

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 coadministered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

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

4.6 Pregnancy and lactation

Pregnancy

Safety and efficacy of Rivaroxaban tablets 15/20 mg 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 tablets 15/20 mg is contraindicated during pregnancy.

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of Rivaroxaban tablets 15/20 mg have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rivaroxaban tablets 15/20 mg 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

Tabulated list of adverse reactions

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

Frequencies are defined as:

Very common (≥ 1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000) not known (cannot be estimated from the available data)

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

	dermatitis allergic, Angioedema and allergic oedema		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	Dry mouth			

and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]				
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	Haemarthrosis	Muscle		Compartment

extremity[A]		haemorrhage		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.

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. 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. 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.

4.9 Overdose

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions.

There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available for adults, but not established in children (refer to the Summary of Product Characteristics of andexanet alfa).

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter. 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 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 adults and in children receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings.

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

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

Mechanism of action

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

5.2 Pharmacokinetic properties

Absorption

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

Oral absorption of Rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect Rivaroxaban AUC or C_{max} at the 2.5 mg and 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When 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 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

In adults,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

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

In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

Inter-ethnic differences

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

In adults, there was an increase in Rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, Rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding Rivaroxaban is not expected to be dialysable. Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

Paediatric population

Safety and efficacy have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (postimplantation 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.

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

6. Pharmaceutical particulars

6.1 List of Excipients

Tablet core
Microcrystalline Cellulose Lactose monohydrate Croscarmellose Sodium
Colloidal Silicon Dioxide
Hydroxypropyl methylcellulose
Sodium lauryl Sulphate Magnesium Stearate
Film Coating
Instacoat universal brown
A05G12657

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

7 tablets packed in white opaque PVC/PE/PVdC blister pack. Such 4 Blister packed in a carton along with pack insert.

6.6 Special Precaution for disposal

No special requirements.

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

7. Supplier

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9. Date of authorization

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10. Date of Revision of the Text:

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