

For the use of a Registered Medical Practitioner only

1. Generic Name

Rivaroxaban Tablets 10 mg

RIVAXA® 10

Rivaroxaban Tablets 15 mg

RIVAXA® 15

Rivaroxaban Tablets 20 mg

RIVAXA® 20

2. Qualitative and Quantitative Composition

Rivaxa 10mg

Each film coated tablet contains:

Rivaroxaban Ph.Eur 10 mg

Excipients q.s.

Colours: Red Oxide of Iron and Titanium Dioxide I.P.

Rivaxa 15mg

Each film coated tablet contains:

Rivaroxaban Ph.Eur 15 mg

Excipients q.s.

Colours: Red Oxide of Iron and Titanium Dioxide I.P.

Rivaxa 20mg

Each film coated tablet contains:

Rivaroxaban Ph.Eur..... 20 mg

Excipients..... q.s.

Colours Red Oxide of Iron and Titanium Dioxide I.P.

3. Dosage Form & Strength

Refer section 1 & 2

4. Clinical Particulars

4.1 Therapeutic Indications

1. For the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.
2. Treatment of deep vein thrombosis and for prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).
3. For the prevention of stroke and systemic embolism in patient with non-valvular arterial fibrillation.

4.2 Posology and Method of administration

Posology

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established.

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

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

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

Treatment of deep vein thrombosis and for prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE)

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

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

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

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

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

The 4-week treatment initiation pack of rivaroxaban is dedicated to patients who will transition from 15 mg twice daily to 20 mg once daily from Day 22 onwards.

For patients with moderate or severe renal impairment where the decision has been taken for 15 mg once daily from Day 22 onwards, other pack sizes only containing 15 mg film-coated tablets are available.

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.

For the prevention of stroke and systemic embolism in patient with non-valvular arterial fibrillation

The recommended dose is 20 mg once daily.

For patients with moderate renal impairment (creatinine clearance (CrC): <50-30mL/min) the recommended dose is 15 mg once daily

Therapy should be continued as long as risk factors for stroke and systemic embolism persist.

Method and frequency of administration

One 20 mg tablet of rivaroxaban should be taken once daily.

For patients with moderate renal impairment (CrC): <50-30mL/min) one 15 mg tablet of rivaroxaban should be taken once daily.

Rivaroxaban 15 mg tablets and 20 mg tablets should be taken with food.

For patients who are unable to swallow whole tablets, rivaroxaban tablet may be crushed and mix with water or soft foods such as applesauce immediately prior to use and administered orally. After the administration of crushed rivaroxaban 15 mg or rivaroxaban 20 mg tablets, the dose should be immediately followed by food.

The crushed rivaroxaban tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering rivaroxaban. The crushed tablet should be administered in small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed rivaroxaban 15mg or rivaroxaban 20 mg tablets, the dose should be then be immediately followed enteral feeding.

Converting from Vitamin K Antagonists (VKA) to Rivaroxaban

For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and rivaroxaban therapy should be initiated once the International Normalised Ratio (INR) is ≤ 2.5 .

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

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.

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

For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, patients should be treated with 15 mg twice daily for the first 3 weeks.

Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting.

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).

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

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 are to be taken with 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. After the administration of

crushed rivaroxaban 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.

4.3 Contraindications

- Hypersensitivity to the active substance
- 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.

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.

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.

Renal impairment

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

Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

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.

Other haemorrhagic risk factors

As with other anti-thrombotics, 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 the 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.

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

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

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and

symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg or 20 mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban. Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

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

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban 10mg/rivaroxaban 15 mg/ rivaroxaban 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 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 Interactions

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.

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

Pregnant women

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.

Lactating women

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.

Pediatric patients

Safety and effectiveness in pediatric patients have not been established.

Geriatric patients

Of the total number of patients in the RECORD 1-3 clinical studies evaluating rivaroxaban, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In the EINSTEIN DVT, PE and Extension clinical studies approximately 37% were 65 years and over and about 16% were >75 years. In EINSTEIN CHOICE, approximately 39% were 65 years and over and about 12% were >75 years. In the MAGELLAN study, approximately 67% were 65 years and over and about 37% were >75 years. In the COMPASS study, approximately 76% were 65 years and over and about 17% were >75 years. In clinical trials the efficacy of rivaroxaban in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients.

Renal Impairment

In pharmacokinetic studies, compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased by approximately 44 to 64% in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Hepatic Impairment

In a pharmacokinetic study, compared to healthy subjects with normal liver function, AUC increases of 127% were observed in subjects with moderate hepatic impairment (Child-Pugh B).

The safety or PK of rivaroxaban in patients with severe hepatic impairment (Child-Pugh C) has not been evaluated.

Avoid the use of rivaroxaban in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

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

The adverse reactions are listed by system organ class, frequency category and grade of severity. Frequency categories are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Common: Anaemia (incl. respective laboratory parameters)

Uncommon: Thrombocytosis (incl. platelet count increased), Thrombocytopenia

Immune system disorders

Uncommon: Allergic reaction, dermatitis allergic, Angioedema and allergic oedema

Very rare: Anaphylactic reactions including anaphylactic shock

Nervous system disorders

Common: Dizziness, headache

Uncommon: Cerebral and intracranial haemorrhage, syncope

Eye disorders

Common: Eye haemorrhage (incl. conjunctival haemorrhage)

Cardiac disorders

Uncommon: Tachycardia

Vascular disorders

Common: Hypotension, haematoma

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis, haemoptysis

Gastrointestinal disorders

Common: Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting

Uncommon: Dry mouth

Hepatobiliary disorders

Common: Increase in transaminases

Uncommon: Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase, increased GGT

Rare: Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)

Skin and subcutaneous tissue disorders

Common: Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage

Uncommon: Urticaria

Very rare: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome

Musculoskeletal and connective tissue disorders

Common: Pain in extremity

Uncommon: Haemarthrosis

Rare: Muscle haemorrhage

Not known: Compartment syndrome secondary to a bleeding

Renal and urinary disorders

Common: Urogenital tract haemorrhage (incl. haematuria and menorrhagia), renal impairment (incl. blood creatinine increased, blood urea increased)

Not known: Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion

General disorders and administration site conditions

Common: Fever, peripheral oedema, decreased general strength and energy (incl. Fatigue and asthenia)

Uncommon: Feeling unwell (incl. malaise)

Rare: Localised oedema

Investigations

Uncommon: Increased LDH, increased lipase, increased amylase

Injury, poisoning and procedural complications

Common: Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion

Rare: Vascular pseudoaneurysm

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs.

For Product Complaints/Adverse events or Queries please write to webmasterindia@abbott.com

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 rivaroxaban 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 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 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

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

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

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).

Elimination

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.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

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

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

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/ progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

7. Description

RIVAXA® 10 :

RIVAXA 10 is supplied for oral administration, as a film coated tablet of Rivaroxaban. Each film coated tablet of RIVAXA 10 contains Rivaroxaban 10 mg.

RIVAXA® 15 :

RIVAXA 15 is supplied for oral administration, as a film coated tablet of Rivaroxaban. Each film coated tablet of RIVAXA 15 contains Rivaroxaban 15 mg.

RIVAXA® 20 :

RIVAXA 20 is supplied for oral administration, as a film coated tablet of Rivaroxaban. Each film coated tablet of RIVAXA 20 contains Rivaroxaban 20 mg.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None

8.2 Shelf-life

Refer pack

8.3 Packing Information

Refer pack

8.4 Storage Condition and handling instructions

Refer pack

9. Patient Counselling Information

Remind patients to not discontinue rivaroxaban without first talking to their healthcare professional.

Advise patients with atrial fibrillation to take rivaroxaban once daily with the evening meal.

Advise patients for initial treatment of DVT and/or PE to take rivaroxaban 15 mg or 20 mg tablets with food at approximately the same time every day.

Advise patients who are at a continued risk of recurrent DVT and/or PE after at least 6 months of initial treatment, to take rivaroxaban 10 mg once daily with or without food.

Advise patients who cannot swallow the tablet whole to crush rivaroxaban and combine with a small amount of applesauce followed by food.

For patients requiring an NG tube or gastric feeding tube, instruct the patient or caregiver to crush the rivaroxaban tablet and mix it with a small amount of water before administering via the tube.

If a dose is missed, advise the patient to take rivaroxaban as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

Bleeding Risks

Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with rivaroxaban.

If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, advise the patient to contact his or her physician immediately.

Invasive or Surgical Procedures

Instruct patients to inform their healthcare professional that they are taking rivaroxaban before any invasive procedure (including dental procedures) is scheduled.

Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions

Pregnancy and Pregnancy-Related Hemorrhage

Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with rivaroxaban

Advise pregnant women receiving rivaroxaban to immediately report to their physician any bleeding or symptoms of blood loss.

Lactation

Advise patients to discuss with their physician the benefits and risks of rivaroxaban for the mother and for the child if they are nursing or intend to nurse during anticoagulant treatment

Females and Males of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician

10. Details of Manufacturer

Refer Pack for manufacturer details.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 6 &

11 to 16 Ground Floor, 101 to 106 &

111 to 116 First Floor, 201 to 206 & 211 to 216

2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, India.

11. Details of permission or licence number

Refer Pack for Permission/License details

12. Date of revision

Version 4.0, dated 07th Nov 2023