Rixalta® 15 & 20

Rivaroxaban

FORMS AND PRESENTATION
Rixalta® 15: Film Coated Tablet; Box of 30.
Rixalta® 20: Film Coated Tablet; Box of 30.

COMPOSITION
Rixalta® 15: Each film Coated Tablet contains 15mg of Rivaroxaban.
Excipients: Lactose monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Hydroxypropyl Methyl Cellulose, Sodium Lauryl Sulfate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, Red Iron Oxide Non IRR.
Rixalta® 20: Each film Coated Tablet contains 20mg of Rivaroxaban.
Excipients: Lactose monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Hydroxypropyl Methyl Cellulose, Sodium Lauryl Sulfate, Magnesium Stearate, Hypromellose, Titanium Dioxide, Macrogol, Red Iron Oxide Non IRR.

PHARMACOLOGICAL PROPERTIES
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.
Pharmacokinetic properties
Absorption
Rivaroxaban is rapidly absorbed with maximum concentrations (Cmax) appearing 2 - 4 hours after tablet intake.
Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or Cmax at the 2.5 mg and 10 mg dose.
Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When Rixalta® 20 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. Rixalta® 15 and Rixalta® 20 are to be taken with food.
Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions Rixalta® 10, 15 and 20 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 Cmax 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 Cmax) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.
Distribution
Plasma protein binding in humans is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 litres.
Biotransformation and elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.
Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on in vitro investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

INDICATIONS
- 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.

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.

PRECAUTIONS
Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.
Haemorrhagic risk
As with other anticoagulants, patients taking Rixalta® are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Rixalta® 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. Rixalta® 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.
Rixalta® should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.
Other haemorrhagic risk factors
As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding
Patients with prosthetic valves
Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Rixalta® have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Rixalta® provides adequate anticoagulation in this patient population. Treatment with Rixalta® 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 non-valvular 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
Rixalta® 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 Rixalta® 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 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, Rixalta® 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.
Rixalta® 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
Rixalta® contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Effects on ability to drive and use machines
Rixalta® 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.

FERTILITY, PREGNANCY AND LACTATION
Pregnancy
Safety and efficacy of Rixalta® 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, Rixalta® is contraindicated during pregnancy.
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.
Breast-feeding
Safety and efficacy of Rixalta® have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Rixalta® 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.

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 Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Rixalta® 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. (For patients with renal impairment).
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. (For patients with renal impairment).
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 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 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.

ADVERSE EFFECTS

The frequencies of adverse reactions reported with Rixalta® are summarised below by frequency.

Common (≥ 1/100 to < 1/10)
- Anaemia (incl. respective laboratory parameters)
- Dizziness, headache
- Eye haemorrhage (incl. conjunctival haemorrhage)
- Hypotension, haematoma
- Epistaxis, haemoptysis
- Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting
- Increase in transaminases
- Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage
- Pain in extremity
- Urogenital tract haemorrhage (incl. haematuria and menorrhagia), renal impairment (incl. blood creatinine increased, blood urea increased)
- Fever, peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)
- Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion

Uncommon (≥ 1/1,000 to < 1/100)
- Thrombocytosis (incl. platelet count increased), Thrombocytopenia
- Allergic reaction, dermatitis allergic, Angioedema and allergic oedema
- Cerebral and intracranial haemorrhage, syncope
- Tachycardia
- Dry mouth
- Hepatic impairment, Increased bilirubin, increased blood alkaline phosphatase, increased GGT
- Urticaria
- Haemarthrosis
- Feeling unwell (incl. malaise)
- Increased LDH, increased lipase, increased amylase

Rare (≥ 1/10,000 to < 1/1,000)
- Jaundice, Bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (incl. hepatocellular injury)
- Muscle haemorrhage
- Localised oedema
- Vascular pseudoaneurysm

Very rare (< 1/10,000)
- Anaphylactic reactions including anaphylactic shock
- Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS syndrome

Not known (cannot be estimated from the available data)
- Compartment syndrome secondary to a bleeding
- Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion

DOSAGE AND ADMINISTRATION

Dosage

• Prevention of stroke and systemic embolism

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

Therapy with Rixalta® 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 Rixalta® 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

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 Rixalta®10 once daily, a dose of Rixalta® 20 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 Rixalta® 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 Rixalta® immediately to ensure intake of 30 mg Rixalta® 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 Rixalta® immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Rixalta®

For patients treated for prevention of stroke and systemic embolism, VKA treatment should be stopped and Rixalta® therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.

For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and Rixalta® therapy should be initiated once the INR is ≤ 2.5.

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

Converting from Rixalta® to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from Rixalta® to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Rixalta® can contribute to an elevated INR.

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

Converting from parenteral anticoagulants to Rixalta®

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rixalta® 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 Rixalta® to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next Rixalta® 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, Rixalta® 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 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

Rixalta® 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 Rixalta® in children aged 0 to 18 years have not been established. No data are available. Therefore, Rixalta® is not recommended for use in children below 18 years of age.

Patients undergoing cardioversion

Rixalta® can be initiated or continued in patients who may require cardioversion.

For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rixalta® 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 Rixalta® 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 Rixalta® once daily (or 10 mg Rixalta® 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.

Method of administration

Rixalta® is for oral use.

The tablets are to be taken with food.

For patients who are unable to swallow whole tablets, Rixalta® tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed Rixalta®15 or 20 film-coated tablets, the dose should be immediately followed by food.

The crushed Rixalta® tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Rixalta® 15 or 20 film-coated tablets, the dose should then be immediately followed by enteral feeding.

OVERDOSAGE

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.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of Revision: November 2020.

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

Benta S.A.L.
Dbayeh - Lebanon