Guide for doctors with information on the use of the drug Rufixalo® (rivaroxaban)

This Guide represents educational material that is mandatory as a condition for placing the drug Rufixalo on the market, with the aim of additional minimization of the important selected risks.

Without promotional content.

The information provided in this educational material does not replace information provided in the instructions for the use of the drug (general description of the drug). For complete information before using the medicine, please read instructions for use of the drug (available on the website http://www.pharm.am, in the information section of registered drugs)

This educational material can be found in " *Center of Drug and Medical Technology Expertise* " on the CJSC website, in the News and Announcements section (drug safety control)

Summary of important risks and recommended measures to prevent and/or minimize risks

- Details of populations that may have a higher risk of bleeding.
- Dose reduction recommendations in at-risk populations.
- Guidelines for switching from and to Rufixalo therapy.
- Necessity to use Rufixalo 15 mg and 20 mg tablets with food.
- Treatment in case of drug overdose.
- Application of coagulation tests and their interpretation.
- Need for explaining to patients:
    - signs and symptoms of bleeding and when to ask for medical help;
    - the importance of adherence to therapy;
    - necessity to take the 15 mg and 20 mg tablets with food;
    - the need to always carry the Card for the patient, which is included in each package of the medicine;
    - the need to inform healthcare professionals that they are using the drug Rufixalo before surgery or before an invasive procedure.

Contents

A guide for doctors

In this Guide for Doctors there are recommendations for the use of the drug Rufixalo, which would minimize the risk of bleeding during therapy with this drug. The information provided in this Guide for Physicians does not replace that provided in the Summary of Product Characteristics.

Before prescribing please read Summary of Product Characteristics.

Patient alert card

Every patient who is prescribed with Rufixalo will receive a Patient Card, which is available in each package of the medicine.

To each patient and guardian should be explained the possible consequences of anticoagulant therapy and the importance of adherence to therapy,the signs of bleeding and when to call for medical help.

The patient alert card is intended to inform the physician and dentist about the patient's anticoagulant therapy and contains emergency contact information. The patient must be informed that he should always carry the Patient Card and show it to every healthcare professional.

Dosage recommendations

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation

Recommended dose for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation is 20 mg once daily.

Dosing scheme

Continuous therapy

Rufixalo 20 mg once daily* **To be taken with food**

* For the recommended dosing scheme in patients with atrial fibrillation and moderate or severe renal impairment see below.

Patients with impaired renal function

In patients with moderate (creatinine clearance 30 – 49 ml/min) or severe (creatinine clearance 15 – 29 ml/min) impaired renal function, the recommended dose is 15 mg once a day. Rufixalo should be used with caution in patients with severe renal impairment (creatinine clearance 15 – 29 ml/min) and its use is not recommended in patients with creatinine clearance < 15 ml/min.

Rufixalo should be used with caution in patients with impaired renal function who are concurrently receiving other drugs that increase plasma concentrations of rivaroxaban.

Duration of therapy

Therapy with the drug Rufixalo must be applied long-term if the benefit of stroke prevention is bigger than the risk of bleeding.

Missed dose

If the patient misses a dose, he must take Rufixalo immediately and from the next day to continue taking the drug once a day as prescribed. It is not allowed take 2 doses during the same day in order to make up for the missed dose.

Patients with nonvalvular atrial fibrillation undergoing percutaneous coronary intervention (PCI - percutaneous coronary intervention) with stent implantation

There is limited experience with reduced doses of Rufixalo 15 mg once daily (or Rufixalo 10 mg once daily, for patients with moderately impaired renal function (creatinine clearance 30 – 49 ml/min)) in addition with the use of a P2Y12 receptor inhibitor, up to a maximum of 12 months, in patients with non-valvular atrial fibrillation requiring oral anticoagulant therapy and undergoing PCI with stent implantation.

Patients undergoing cardioversion

Rufixalo therapy may be initiated or continued in patients who may require cardioversion.

For cardioversion guided by transesophageal echocardiography (TEE) in patients who previously were not treated with anticoagulants, Rufixalo therapy should be initiated at least 4 hours prior to cardioversion to ensure adequate anticoagulation. Before cardioversion, all patients must be asked to confirm that they have taken Rufixalo as prescribed. When the decision on the initiation of therapy and duration, the recommendations of the current guidelines for anticoagulant therapy in patients undergoing cardioversion must be taken into account.

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

Patients initially take 15 mg twice a day for the first three weeks. After initial therapy, patients take 20 mg once daily as continuous therapy.

When prolonged prevention of recurrent DVT or BE is indicated (after completion of at least 6 months of therapy for deep vein thrombosis or pulmonary embolism), the recommended dose is 10 mg **once a day**. In patients considered to be at high risk of recurrent DVT or PE, such as those with complicated comorbidities or those in whom recurrent DVT or PE has occurred during prolonged prophylaxis with Rufixalo 10 mg **once a day**, it is necessary to consider taking the drug Rufixalo in a dose of 20 mg **once a day**.

Rufixalo 10 mg is not recommended as initial therapy for DVT and for PE within the first 6 months of treatment.

Dosing scheme

1. – 21. day	from the 22nd day onwards	After completing at least 6 months of treatment
Rufixalo from 15 mg twice a day*	Rufixalo from 20 mg once a day*	Rufixalo from 20 mg once a day * OR Rufixalo from 20 mg once a day *

In patients considered to be at high risk of recurrent DVT/BE (such as those with complicated comorbidities or in whom recurrent DVT or BE has occurred during prolonged prophylaxis with 10 mg once daily), it is necessary to consider taking the drug Rufixalo in a dose of 20 mg once a day .

Rufixalo 10mg tablets: MAY BE TAKEN WITH OR WITHOUT FOOD. Rufixalo 15 and 20 mg tablets: MUST BE TAKEN WITH FOOD.

*For recommended dosing scheme in patients with DVT or BE and moderate or severe renal impairment see below.

Patients with impaired renal function

Patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) impaired renal function treated for acute DVT, of acute PE and prevention of recurrent DVT and PE must take 15 mg twice a day for the first three weeks.

After that, the recommended dose is 20 mg once a day. Dose reduction from 20 mg once a day to 15 mg once a day must be considered for the patient when the estimated risk of bleeding exceeds the risk of recurrent DVT and PE. The recommendation for taking 15 mg is based on pharmacokinetics model and has not been tested under these clinical conditions. Rufixalo must be administered with caution in patients with severely impaired renal function (creatinine clearance 15-29 ml/min) and is not recommended in patients with creatinine clearance < 15 ml/min. When the recommended dose is 10 mg once a day (after at least 6 months of therapy), no adjustment of the recommended daily dose is necessary.

Rufixalo must be used with caution in patients with impaired renal function[1] who concomitantly receive other drugs that increase concentrations rivaroxaban in plasma.

Duration of therapy

It is necessary to consider a short duration of treatment (at least 3 months) in patients with DVT and PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of treatment should be considered in patients with unprovoked DVT or PE associated with major transient risk factors, unprovoked DVT or PE or history of recurrent DVT or of PE.

Missed dose

- Dosing period twice a day (15 mg twice a day for the first 3 weeks): If the patient misses a dose, he must take Rufixalo immediately to ensure that the daily dose of Rufixalo is 30 mg. In this case, two 15 mg tablets can be taken at once. Next day patient should continue with regular 15 mg twice daily as recommended.
- Dosing period once a day (after three weeks): If the patient misses a dose, he should immediately take Rufixalo and from the next day continue to take the medicine as recommended – once a day. The dose should not be doubled during the same day to make up for the missed dose.

[1] with moderately impaired renal function (creatinine clearance 30-49 ml/min) for Rufixalo 10 mg

Prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) and at high risk of ischemic events

Dosing scheme

Individual duration of treatment

Rufixalo 2.5 mg twice a day

Rufixalo 2.5mg CAN BE TAKEN WITH OR WITHOUT FOOD.

Patients taking Rufixalo 2.5 mg twice daily must also take 75 to 100 mg of acetylsalicylic acid (ASA) a day.

In patients with successfully performed revascularization of lower limb (by surgical or endovascular procedure, including combined procedure) due to symptomatic PAD, treatment should not be started before hemostasis is achieved (see also section 5.1 of the Summary of Product Characteristics).

Patients with impaired renal function

No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30 – 49 ml/min). Rufixalo should be used with caution in patients with severe impairment of renal function (creatinine clearance 15-29 ml/min). It is not recommended use of the drug in patients with creatinine clearance < 15 ml/min.

In patients with moderate impairment of renal function (creatinine clearance of 30 to 49 ml/min), who concurrently use other drugs that increase the concentration of rivaroxaban in plasma, Rufixalo should be used with caution.

Duration of therapy

The duration of treatment should be determined individually for each patient based on regular controls, considering the risk of thrombotic events versus risk of bleeding.

Concurrently use with antiplatelet therapy

In patients with an acute thrombotic event or vascular interventions who requiring dual antiplatelet therapy, continuation of the administration of the drug Rufixalo 2.5 mg twice daily should be evaluated depending on the type of event or interventions and antiplatelet therapy.

Special warnings and precautions for use in patients with CAD / PAD

In patients with CAD / PAD at high risk of ischemic events, efficacy and safety of the drug Rufixalo 2.5 mg twice daily are tested in combination with ASA.

In patients who recently underwent revascularization procedure of the lower limb due to symptomatic PAD, the efficacy and safety of Rufixalo at a dose of 2.5 mg twice daily have been studied in combination with antiplatelet drugs: ASA alone or ASA with additional short-term administration of clopidogrel. If necessary, dual antiplatelet therapy with clopidogrel should be short-term, long-term dual antiplatelet therapy should be avoided. Patients who recently underwent a successful revascularization procedure of the lower limb (by surgical or endovascular intervention, including combined procedure) due to symptomatic PAD was allowed additionally to use standard dose of clopidogrel once a day for a maximum of 6 months (see also section 5.1 of the Summary of Product Characteristics).

Treatment in combination with other antiplatelet drugs, e.g prasugrel or ticagrelor has not been tested and is not recommended.

Concurrently treatment of CAD / PAD with Rufixalo 2.5 mg and ASK is contraindicated in patients with previous hemorrhagic or lacunar stroke or any type of stroke in the last month. Treatment with Rufixalo 2.5 mg should be avoided in patients with a previous stroke or transient ischemic attack (TIA) receiving dual antiplatelet therapy.

If Rufixalo is administered with ASA, it should be used with caution in patients with CAD/PAB:

- aged ≥ 75 years. The benefit-risk ratio of treatment for each patient should be regularly assessed.
- with lower body weight (< 60 kg).
- in patients with CAD who have severe symptomatic heart failure. Trial data suggest that such patients may benefit less from treatment with Rufixalo (see section 5.1 of the Summary of Product Characteristics for further clarification).

Missed dose

If a dose is missed, the patient should continue taking the recommended dose of Rufixalo 2.5 mg according to the schedule. The dose should not be doubled to make up for a missed dose.

Prevention of atherothrombotic events in adult patients after acute coronary syndrome (ACS) with elevated cardiac biomarkers

Dosing scheme

Individual duration of treatment

Rufixalo 2.5 mg twice a day

Rufixalo 2.5mg CAN BE TAKEN WITH OR WITHOUT FOOD.

Additionally, with Rufixalo 2.5 mg, patients must take a daily dose of 75-100 mg of acetylsalicylic acid or the daily dose of acetylsalicylic acid 75-100 mg in addition to a daily dose of 75 mg of clopidogrel or usual daily doses of ticlopidine.

The recommended starting dose of Rufixalo is 2.5 mg twice a day and should be started as soon as possible after the stabilization of the acute coronary syndrome, and at the earliest on the 24 hours after admission to the hospital and at the time when parenteral anticoagulation would be required therapy was usually discontinued.

Patients with impaired renal function

No dose adjustment is required in patients with moderate renal impairment (creatinine clearance 30 – 49 ml/min). Rufixalo should be used with caution in patients with severe renal impairment (creatinine clearance 15 – 29 ml/min), and its use is not recommended in patients with creatinine clearance < 15 ml/min.

In patients with moderate impairment of renal function (creatinine clearance 30–49 ml/min), who concurrently use other drugs that increase the concentration of rivaroxaban in plasma, Rufixalo should be used with caution.

Duration of therapy

The duration of treatment should be determined individually in each patient based on regular controls, considering the risk of ischemic events and the risk of bleeding. Long-term treatment beyond 12 months must be decided for each patient individually, because the experience of application up to 24 months is limited.

Concurrently use with antiplatelet therapy

In patients with an acute thrombotic event or vascular interventions who requiring dual antiplatelet therapy, continuation of the administration of the drug Rufixalo 2.5 mg twice

daily should be evaluated depending on the type of event or interventions and antiplatelet therapy.

Special warnings and precautions for use in patients with ASC

Efficacy and safety of Rufixalo 2.5 mg twice daily in patients with recent acute coronary syndrome were investigated in in combination with antiplatelet drugs: with ASA or ASA in addition clopidogrel/ticlopidine.

Treatment in combination with other antiplatelet drugs, e.g. prasugrel or ticagrelor has not been tested and is not recommended.

Caution is required when using Rufixalo with ASA or with ASA with the addition of clopidogrel or ticlopidine, in patients with ACS:

- at the age of ≥ 75 years. The benefit-risk ratio of treatment for each patient should be regularly assessed.
- less body weight (< 60 kg)

Concomitant treatment of ACS with Rufixalo and antiplatelet drugs it is contraindicated in patients with a previous stroke or transient ischemic attack (TIA).

Missed dose

If a dose is missed, the patient should continue taking the recommended dose of Rufixalo 2.5 mg according to the schedule. The dose should not be doubled to make up for a missed dose.

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective surgical procedure of implanting an artificial hip or knees

The recommended dose is Rufixalo 10 mg orally once a day. The first dose must be taken 6-10 hours after surgery, considering that hemostasis has been established.

Duration of therapy

The duration of treatment depends on the patient's individual risk for developing venous thromboembolism, which is determined by the type of orthopedic surgery.

- Recommended duration of treatment for patients undergoing major hip surgery, the recommended duration of therapy is 5 weeks.
- Recommended duration of treatment for patients undergoing major knee surgery, the recommended duration of therapy is 2 weeks

Missed dose

If a dose is missed, the patient must take Rufixalo immediately, and the next day to continue taking the medicine once a day as before.

Oral administration

Rufixalo 2.5 mg and 10 mg tablets can be taken with or without food.

Rufixalo 15 mg and 20 mg must be taken with food. Taking these doses at the same time as food ensures the necessary absorption of the drug and thus ensures high bioavailability after oral administration.

For patients who cannot swallow the whole tablet, the Rufixalo tablet can crush and mix with water or applesauce immediately before taking and apply orally. After administration of crushed Rufixalo 15 mg or 20 mg film-coated, the dose should be immediately followed by food.

A crushed Rufixalo tablet can be given through a gastric tube, after confirming that the tube is properly placed in the stomach. The crushed tablet should be given with a small amount of water through the gastric tube, and then the tube should be flushed with water. After administration of crushed Rufixalo 15 mg or 20 mg film-coated tablet, the dose should be immediately followed by food.

Use of the drug during surgical intervention

If an invasive procedure or surgical intervention is required, if possible and based on the physician's clinical assessment:

 Rufixalo tablets of 10, 15 and 20 mg must be discontinued at least 24 hours before the intervention.

 Rufixalo 2.5 mg tablets must be discontinued at least 12 hours before the intervention if possible and based on the physician's clinical assessment. If intervention cannot be delayed, the increased risk of bleeding must be assessed against urgency of intervention.

Administration of the drug Rufixalo must be continued as soon as possible after the invasive procedure or surgical intervention, provided that the clinical situation allows it and adequate hemostasis has been established.

Spinal/epidural anesthesia or puncture

During neuraxial anesthesia (spinal/epidural anesthesia) or during spinal/epidural puncture, patients treated with antithrombotic drugs for the prevention of thromboembolic complications have a high risk of developing an epidural or spinal hematoma, which can lead to long-term or permanent paralysis. The risk of these events may increase with the postoperative use of permanent epidural catheters or with the concurrently use of drugs that affect hemostasis. This risk may also increase with traumatic or repeated epidural or spinal puncture. Patients should be observed frequently for signs and symptoms of neurological disorders (eg, numbness or weakness of the legs, bowel or bladder dysfunction). If a neurological disorder is observed, it should be diagnosed and treated immediately. Before neuraxial intervention, the physician should perform an assessment of the potential benefit versus risk in patients on anticoagulant therapy or in patients who should receive anticoagulant therapy for thromboprophylaxis.

Recommendations for specific indications

- **Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation**
- **Treatment of DVT and PE and prevention of recurrent DVT and PE in adult patients**

There is no clinical experience with the use of Rufixalo 15 mg and 20 mg tablets in adult patients in these situations. To reduce the potential risk of bleeding associated with concomitant using Rufixalo and neuraxial (epidural/spinal) anesthesia or spinal puncture, the pharmacokinetic profile of rivaroxaban must be considered. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rufixalo is assessed as low. However, the exact time required to achieve sufficiently low anticoagulation effect in each patient is unknown and it needs to be evaluated in relation to the urgency of the diagnostic procedure.

For epidural catheter removal and based on general pharmacokinetics characteristic, it must pass at least twice the half-time, or at least 18 hours in younger adult patients and 26 hours in older patients from the last one administration of Rufixalo (see section 5.2 of the Summary of Product Characteristics). After removal of the catheter, at least 6 hours must pass before the administration of the next dose of the drug Rufixalo. If a traumatic puncture occurs, administration of Rufixalo must be postpone for 24 hours.

- **Prevention of VTE in adult patients undergoing elective surgical procedure of implanting an artificial hip or knee**

To reduce the potential risk of bleeding associated with concomitant use of Rufixalo and neuraxial (epidural/spinal) anesthesia or spinal puncture, the pharmacokinetic profile of Rufixalo must be considered.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rufixalo is assessed as low (see section 5.2 of the Summary of Product Characteristics).

Before removing the epidural catheter, at least 18 hours must pass since the last administration of Rufixalo. After removal of the catheter, at least 6 hours must pass before the administration of the next dose of the drug Rufixalo. If a traumatic puncture occurs, administration of Rufixalo must be postpone for 24 hours.

- **Prevention of atherothrombotic events in adult patients who have coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) with a high risk of ischemic events**
- **Prevention of atherothrombotic events in adult patients after acute coronary syndrome (ACS) with elevated cardiac biomarkers**

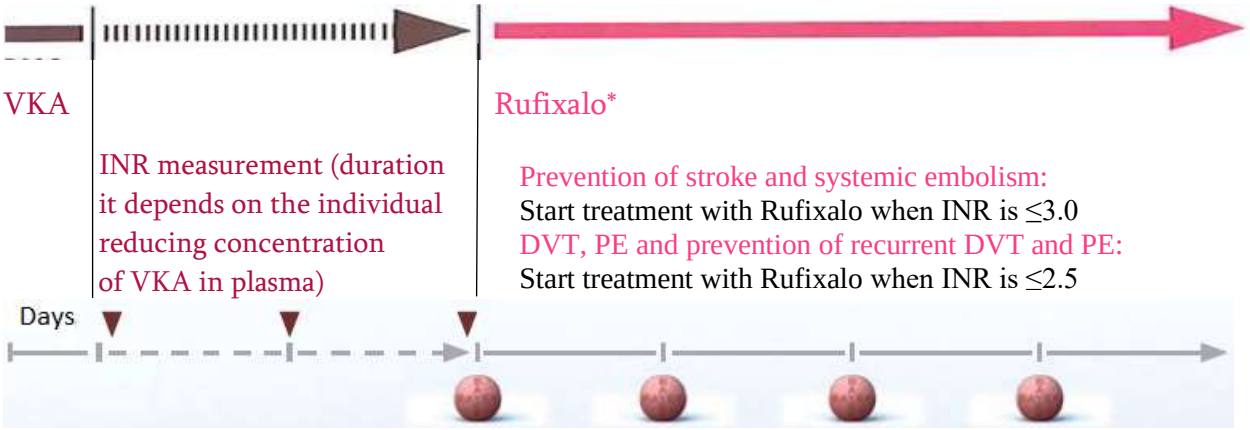
There is no clinical experience with the use of Rufixalo 2.5 mg and antiplatelet agents medicines in these situations. Use of platelet aggregation inhibitors it is necessary to terminate in accordance with the manufacturer's recommendations listed in information about the drug.

To reduce the potential risk of bleeding associated with concomitant using Rufixalo and neuraxial (epidural/spinal) anesthesia or spinal puncture, the pharmacokinetic profile of Rufixalo must be considered.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Rufixalo is assessed as low (see section 5.2 of the Summary of Product Characteristics). However, the exact time required for achieving a sufficiently low anticoagulation effect in every patient is not known.

Switching patients from vitamin K antagonists (VKA) to Rufixalo

Switching patients from VKA to Rufixalo



*See dosage recommendation for required daily dose

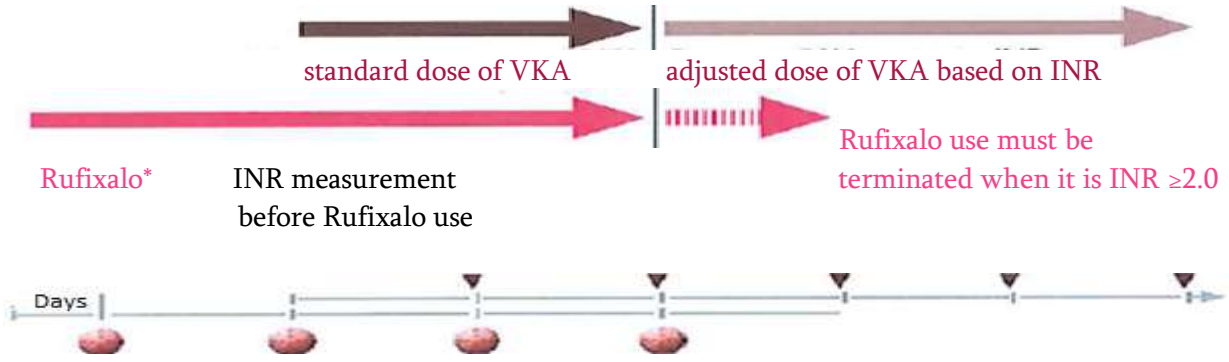
In patients who are taking drugs for the **prevention of stroke and systemic embolism**, treatment with vitamin K antagonists must be stopped and treatment started with Rufixalo when the INR is ≤ 3.0.

In patients who are being treated for **deep vein thrombosis, pulmonary embolism and prevention of recurrent deep vein thrombosis and pulmonary embolism** treatment with vitamin K antagonists must be stopped and treatment started with Rufixalo when the INR is ≤ 2.5.

INR measurement is not suitable for measuring anticoagulant activity of Rufixalo, and therefore we should not be used for this purpose. Treatment with medicine alone Rufixalo does not require routine monitoring of coagulation parameters.

Switching patients from Rufixalo to VKA

Switching patients from Rufixalo to VKA



*See dosage recommendation for required daily dose

It is important to ensure adequate anticoagulation by minimizing the risk of bleeding when switching from one therapy to another.

When switching to VKA, Rufixalo and VKA must be given simultaneously until the INR is ≥ 2.0. During the first two days of the transition period, the standard initial dose of VKA should be administered, followed by VKA dosing based on the results of the INR test.

INR measurement is not suitable for determining the anticoagulant activity of the drug Rufixalo. When patients use Rufixalo and VKA simultaneously, the INR should not be measured earlier than 24 hours after the previous dose, but must be determined before taking the next dose of Rufixalo. When treatment with Rufixalo is stopped, I INR values measured at least 24 hours after the last dose reflect the dose of VKA.

Switching patients from parenteral anticoagulant to Rufixalo

• Patients on parenteral medication with a fixed dosage regimen, such as low-molecular-weight heparin: stop the parenteral drug and start with Rufixalo 0-2 hours before the next scheduled administration time of the parenteral drug.

• Patients who continuously receive parenteral medicine such as intravenous unfractionated heparin: start taking the drug Rufixalo at the time of stopping.

Switching patients from Rufixalo to parenteral anticoagulants

The first dose of the parenteral anticoagulant must be given at the same time as the next dose of Rufixalo.

Populations with potentially higher risk of bleeding

Rufixalo, like other anticoagulants, can increase the risk of bleeding.

That is why Rufixalo is contraindicated in patients:

- with active clinically significant bleeding
- with a lesion or condition, if it is considered to carry a significant risk of major bleeding. This may include an existing or recent gastrointestinal ulcer, the presence of malignant neoplasms with a high risk of bleeding, recent brain or spinal cord injury, recent brain, spinal or eye surgery, recent intracranial bleeding, confirmed or suspected esophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- simultaneously treated with any other anticoagulant, e.g. unfractionated heparin, low molecular weight heparins (enoxaparin, dalteparin and others), heparin derivatives (fondaparinux and others), oral anticoagulants (warfarin, dabigatran etexilate,

apixaban and others), except in situations of changing anticoagulant therapy or when unfractionated heparin is given in doses necessary to maintain an open central venous or arterial catheter

- with liver disease associated with coagulopathy and a clinically significant risk of bleeding, including patients with cirrhosis of the liver, stages B and C according to Child-Pugh classification

Elderly population: The risk of bleeding increases with age.

Some subgroups of patients have a higher risk of bleeding and must be closely monitored for signs and symptoms of bleeding complications.

The decision to treat these patients must be made after evaluating the benefits of treatment in relation to the risk of bleeding.

Patients with impaired renal function

For adult patients, see "Dosing instructions" for patients with moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) impaired renal function.

Rufixalo must be used with caution in patients with a creatinine clearance of 15- 29 ml/min and in patients with impaired renal function[1] who are simultaneously receiving other drugs that increase rivaroxaban plasma concentrations.

Rufixalo is not recommended for use in patients with creatinine clearance <15 ml/min.

[1] with moderately impaired renal function (creatinine clearance 30-49 ml/min) for Rufixalo 2.5 mg and 10 mg

Patients who concurrently receive other

- Systemic azole antifungals (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir): the use of Rufixalo is not recommended
- It is necessary to pay attention to patients who simultaneously receiving drugs that have an effect on hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and reuptake inhibitors storage serotonin and noradrenaline (SNRIs)
- Patients after ACS and patients with BKA/BPA: patients treated with Rufixalo and antiplatelet drugs may be used at the same time treated with non-steroidal anti-inflammatory drugs only if the benefit is greater from the risk of bleeding

- Interaction with erythromycin, clarithromycin or fluconazole probably it is not clinically significant in most patients, but may be potentially significant in high-risk patients (in case of impaired renal function - see text above)

Patients with other bleeding risk factors

Like other antithrombotic drugs, Rufixalo is not recommended in patients with an increased risk of bleeding, who have:

- with congenital or acquired bleeding disorders
- with uncontrolled severe arterial hypertension
- with another gastrointestinal disease without an active ulcer that can lead to complications with bleeding (e.g. inflammatory bowel disease, esophagitis, gastritis, etc.) gastroesophageal reflux disease)
- with vascular retinopathy
- with bronchiectasis or a history of pulmonary bleeding

Cancer patients

Patients with malignant diseases may simultaneously have an increased risk of bleeding and thrombosis. Assessment of whether the benefit of antithrombotic therapy outweighs the risk of bleeding must be carried out separately for each patient with active malignant disease, and depending on the location of the tumor, antineoplastic therapy and stage of the disease. Tumors located in the gastrointestinal or genitourinary tract were associated with an increased risk of bleeding during drug treatment Rufixalo. In patients with malignant neoplasms with a high risk of bleeding, the use of Rufixalo is contraindicated (for more information, see the text above).

Other contraindications

Rufxalo is contraindicated during pregnancy and lactation. Women of reproductive age must avoid pregnancy while taking Rufixalo. Rufixalo is also contraindicated in case of hypersensitivity to the active substance or one of the excipients substances.

Overdose

Due to limited absorption, maximal effect without further increasing the average plasma exposure is expected at doses that are higher than therapeutic, that is 50 mg of Rufixalo or more in adults. If an overdose occurs, taking activated charcoal can be considered to reduce absorption.

If bleeding complications occur in patients taking Rufixalo, the next dose of Rufixalo should be delayed or the treatment must be stopped in an appropriate manner. The individualized approach to the treatment of bleeding includes:

- symptomatic treatment, such as mechanical compression, surgical intervention, fluid replacement
- hemodynamic support; transfusion of blood products or components
- if the bleeding cannot be controlled by the above measures, it must be considered the use of a specific factor Xa inhibitor (andexanet alfa) or a specific clotting agent such as prothrombin complex concentrate (PCC), activated concentrate prothrombin complex (aPCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience of using these drugs in adult patients.

Due to the high degree of binding to plasma proteins, it is not expected that Rufixalo could be removed from the body by dialysis.

Coagulation tests

Rufixalo does not require routine monitoring of coagulation parameters. However, measurement of blood levels of Rufixalo may be useful in certain situations where information about exposure to Rufixalo may aid in clinical decision-making, such as in overdose and emergency surgery.

Anti-factor Xa tests, with specific rivaroxaban calibrators are currently commercially available to measure rivaroxaban levels. If clinically indicated, then hemostatic status can be determined by prothrombin time (RT) using Neoplastin, as described in the Summary of Product Characteristics.

The values of the following coagulation parameters are elevated: prothrombin time (PV), activated partial thromboplastin time (aPTT) and calculated International Normalized Ratio (INR). INR testing was developed to determine the effects of VKA and is therefore not suitable for measuring the activity of Rufixalo. Dosing and treatment decisions should not be based on INR results, except when switching from Rufixalo to VKA, as previously described.

Overview of dosage in adult patients*

Indication	Dosage	Special populations
Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation[a]	**Rufixalo 20 mg once daily**	Patients with impaired renal function (creatinine clearance 15 – 49 ml/min)[b] – Rufixalo 15 mg once daily. PCI for stent placement maximum period of up to 12 months – Rufixalo 15 mg once daily plus a P2Y12 inhibitor (eg clopidogrel). PCI with stent placement In patients with renal impairment (creatinine clearance 30 – 49 ml/min)[b] Rufixalo 10 mg once daily plus a P2Y12 inhibitor (eg clopidogrel).
Treatment of **DVT and PE**[c] and prevention of recurrent DVT and BE in adult patients	Treatment and prevention of recurrences, from the 1st to the 21st day: Rufixalo 15 mg twice daily Prevention of recurrence, from the 22nd day onwards: Rufixalo 20 mg once daily Extended prevention of recurrences, from the 7th month onwards Rufixalo 10 mg once daily Extended prevention of recurrences, from the 7th month onwards Rufixalo 20 mg once daily in	Patients with impaired renal function (creatinine clearance 15 – 49 ml/min)[b] Treatment and prevention of recurrences, from the 1st to the 21st day: Rufixalo 15 mg twice daily. Then Rufixalo 15 mg once daily instead of Rufixalo 20 mg once daily if the patient assessed bleeding risk outweighs the risk of recurrent DVT or BE. At the recommended dose of Rufixalo 10 mg once a day, no adjustment required

	patients considered to be at high risk of recurrent DVT or BE, such as patients: ▯ with complicated comorbidities; ▯ who have developed recurrent DVT or BE, with prolonged prophylaxis with Rufixalo 10 mg once daily.	doses
Prevention of VTE in adult patients undergoing elective surgical procedure of **implanting an artificial hip or knees**	Rufixalo 10 mg once a day	
Prevention of atherothrombotic events in adult patients with **CAD** or symptomatic **PAD** and at high risk of ischemic events	Rufixalo 2.5 mg twice daily **in combination with acetylsalicylic acid** 75 to 100 mg/day	
Prevention of atherothrombotic events in adult patients **after ACS** with elevated cardiac biomarkers	Rufixalo 2.5 mg twice daily in **combination with standard antiplatelet therapy** (acetylsalicylic acid 75–100 mg/day alone or acetylsalicylic acid 75–100 mg/day with 75 mg/day clopidogrel or standard dose ticlopidine)	

Rufixalo 15 and 20 mg tablets must be taken with food

For patients who cannot swallow the whole tablet, the Rufixalo tablet can crush and mix with water or applesauce immediately before taking and apply orally.

[a] with one or more risk factors, such as congestive heart failure, hypertension, age over 75 years, diabetes mellitus, previous stroke or transient ischemic attack.
[b] Use with caution in patients with creatinine clearance 15 - 29 ml/min and in patients with renal impairment who simultaneously receive other drugs that increase plasma concentrations of rivaroxaban.
[c] It is not recommended as an alternative to unfractionated heparin in patients with PE who are hemodynamically unstable or require thrombolysis or pulmonary embolectomy.

Reporting side effects

After receiving the decision to put the drug on the market, it is important to report suspected side effects of the drug. This allows monitoring the degree of benefit and risk of the drug. You can report the side effects of the medicine to "AKADEMICOS E. GABRIELIAN RESEARCH CENTER FOR DRUGS AND MEDICAL TECHNOLOGIES" CJSC (Republic of Armenia, Yerevan 0051, Komitas avenue 49/5) or by email by visiting the company's website: http://www.pharm.am or by calling the following hotline of the company's pharmaceutical control department: by phone numbers: (+374 10) 20-05-05, (+374 96) 22-05-05

You can also report all adverse reactions to Global Pharmacovigilance of Alkaloid via e-mail (pharmacovigilance@alkaloid.com.mk) and to the Local responsible person for pharmacovigilance in Armenia (rubinaayvazan@yahoo.com.mk). Or to the website of Alkaloid AD Skopje: https://alkaloid.com.mk/report-a-drug-form