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Roxavid Film-Coated Tablets

eVIROX02-var (MY)

DESCRIPTION

Roxavid Film-Coated Tablets 15 mg:
Maroon, circular, biconvex film coated tablets, debossed with "125" on one side and "15" on other side.

Roxavid Film-Coated Tablets 20 mg:
Dark Maroon, circular, biconvex film coated tablets debossed with “126” on one side and “20” on other side.

COMPOSITION

Roxavid Film-Coated Tablets 15 mg:
Each film-coated tablet contains 15 mg rivaroxaban.

Roxavid Film-Coated Tablets 20 mg:
Each film-coated tablet contains 20 mg rivaroxaban.

INDICATIONS

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

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

Paediatric population
Roxavid 15 mg
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Roxavid 20 mg
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

DOSAGE AND ADMINISTRATION

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 Roxavid 10 mg once daily, a dose of Roxavid 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	Maximum 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

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

Treatment of VTE and prevention of VTE recurrence in children and adolescents
Roxavid treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment (see section ‘Pharmacodynamic properties’). The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.

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

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

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to Roxavid
- Prevention of stroke and systemic embolism:
- VKA treatment should be stopped and Roxavid therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3.0.
- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:
- VKA treatment should be stopped and Roxavid therapy should be initiated once the INR is ≤ 2.5.

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

Converting from Roxavid to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Roxavid to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Roxavid can contribute to an elevated INR.

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

Paediatric patients:
Children who convert from Roxavid to VKA need to continue Roxavid for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Roxavid. Co-administration of Roxavid and VKA is advised to continue until the INR is ≥ 2.0. Once Roxavid is discontinued INR testing may be done reliably 24 hours after the last dose (see above and section ‘Interaction with other medicinal products and other forms of interaction’).

Converting from parenteral anticoagulants to Roxavid
For adult and patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Roxavid 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 Roxavid to parenteral anticoagulants
Discontinue Roxavid and give the first dose of parenteral anticoagulant at the time the next Roxavid dose would be taken.

Special populations
Renal Impairment:
Adults:
Limited clinical data for patients with severe renal impairment (creatinine clearance 15-29 ml/min) indicate that rivaroxaban palsma concentrations are significantly increased. Therefore, Roxavid is to be used with caution in patients with severe renal impairment (Creatinine clearance 15 – 29 ml/min). 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 dosage 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).

Paediatric population:
- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m²): no dose adjustment is required, based on data in adults and limited data in paediatric patients.
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m²): Roxavid is not recommended as no clinical data is available.

Hepatic impairment:
Roxavid 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.
For paediatric patients the dose is determined based on body weight.

Gender:
No dose adjustment.

Paediatric population:
The safety and efficacy of Roxavid in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Patients undergoing cardioversion
Roxavid can be initiated or continued in patients who may require cardioversion.

For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Roxavid 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 Roxavid 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 Roxavid once daily (or 10 mg Roxavid 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
For oral use.
Roxavid FC Tablets 15 mg & 20 mg: Taken with food.

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

The crushed Roxavid 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 Roxavid 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding.

Children and adolescents weighing 30 kg to 50 kg
Roxavid is for oral use:
The patient should be advised to swallow the tablet with liquid. It should also be taken with food (see section ‘Pharmacokinetic properties’). The tablets should be taken approximately 24 hours apart.

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

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

The crushed tablet may be given through a nasogastric or gastric feeding tube (see sections ‘Pharmacokinetic properties’).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section ‘List of 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, please refer to “PREGNANCY AND LACTATION” section.

WARNING AND PRECAUTIONS

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

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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.

PREGNANCY AND LACTATION

Pregnancy:
Safety and efficacy of Roxavid have not been established in pregnant women. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Roxavid is contraindicated during pregnancy.
Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding:
Safety and efficacy of Roxavid have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, Roxavid 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.

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

Roxavid 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.

ADVERSE EFFECTS

Summary of the safety profile
The safety of rivaroxaban has been evaluated in thirteen phase III studies in adults including 53,103 patients exposed to rivaroxaban and in two phase II and two phase III paediatric studies including 488 patients. See phase III studies as listed in table 1.

Table 1: Number of patients studied, total daily dose and maximum treatment duration in the Roxavid adult and paediatric phase III studies

Indication	Number of patients*	Total daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10mg	39 days
Prevention of venous thromboembolism in medically ill patients	3997	10mg	39 days
Treatment of DVT, PE and prevention of recurrent DVT, PE	6,790	Day 1 – 21: 30mg Day 22 and onwards: 20mg After at least 6 months: 10mg or 20mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight adjusted dose to achieve aa similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily.	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20mg	41 months
Prevention of atherothrombotic events in patients after an ACS	10,225	5mg or 10mg respectively , in combination with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of stroke, myocardial infarctionand cardiovascular death prevention of acute limb ischemia and mortality in patients with CAD or PAD	18,244	5mg in combination with 100mg ASA or 10mg alone	47 months

*Patients exposed to at least one dose of rivaroxaban

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2).

The most commonly reported bleedings (≥4 %) were epistaxis (5.8 %) and gastrointestinal tract haemorrhage (4.1 %).

In total about 65% of patients exposed to at least one dose of rivaroxaban were reported with treatment emergent adverse events.

About 21 % of the patients experienced adverse events considered related to treatment as assessed by investigators.

Table 2: Bleeding and anaemia event rates in patients exposed to rivaroxaban across the completed phase III studies

Indication	Any Bleeding	Anaemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrence	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment.	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of stroke, myocardial infarction and cardiovascular death, prevention of acute limb ischemia and mortality in patients with CAD or PAD	6.7 per 100 patient years*	0.15 per 100 patient years*

* A pre-specified selective approach to adverse event collection was applied.

Tabulated list of adverse reactions
The frequencies of adverse reactions reported with Xarelto are summarised in table 2 below by system organ class (in MedDRA) and by frequency

Frequencies are defined as:
- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)
- uncommon (≥ 1/1,000 to < 1/100)
- rare (≥ 1/10,000 to < 1/1,000)
- very rare (< 1/10,000)
- not known (cannot be estimated from the available data)

Table 3: All treatment-emergent adverse reactions reported in patients in phase III studies and in two phase II and two phase III studies in paediatric patients

Common	Uncommon	Rare	Not Known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)^		
Immune system disorders			
	Allergic reaction dermatitisallergic		
Nervous system disorders			
Dizziness, headache	Cerebral and intracronial haemorrhage, syncope		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
	Tachycardia		
Vascular disorders			
Hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders			
Epistaxis haemoptysis			
Gastrointestinal disorders			
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation^, diarrhoea, vomiting^	Dry mouth		
Hepatobiliary disorders			
	Hepatic impairment	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalized pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		
Musculoskeletal and connective tissue disorders			
Pain in extremity^	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creastinine increased, blood urea increased)^			Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion.
General disorders and administration site conditions			
Fever^, peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema^	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase^, increased LDH^, increased lipase^, increased amylase^, increased GGT^	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), confusion, wound secretion^		Vascular pseudoaneurysm	

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Haemorrhagic risk
As with other anticoagulants, patients taking Roxavid are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Roxavid 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 adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6-fold on average) which may lead to an increased bleeding risk. Roxavid 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.

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

Roxavid is not recommended in children and adolescents with moderate or severerenal impairmen (glomerular filteration rate < 50 mL/min/1.73 m^2), as no clinical data is available.

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Roxavid should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.
Roxavid is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is available.

Interaction with other medicinal products
The use of Roxavid is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp.

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as 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 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.

Bleeding during antithrombotic treatment may unmask underlying yet unknown malignancy, in particular in the gastrointestinal or genitourinary tract. Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumor location, antineoplastic therapy and stage of disease.

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

Patients with prosthetic valves
Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of Roxavid have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that Roxavid provides adequate anticoagulation in this patient population. Treatment with Roxavid is not recommended for these patients.

Patients with high risk triple positive antiphospholipid syndrome
Roxavid is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome and are persistently triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies) as treatment with rivaroxaban is associated with an increased rate of recurrent thrombotic events compared with vitamin K antagonists (VKA).

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
Roxavid 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 Roxavid 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 Roxavid and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of Roxavid. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of Roxavid is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

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

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

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

Dosing recommendations before and after invasive procedures and surgical intervention
If an invasive procedure or surgical intervention is required, Roxavid 15mg / 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.

Roxavid 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, have been reported during post-marketing surveillance in association with the use of Roxavid. Patients appear to be at highest risk for these reactions early in the course of therapy, with the onset occurring in the majority of cases within the first weeks of treatment. Roxavid 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
Roxavid contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

DRUG INTERATIONS
The extent o interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section ‘Special warnings and precautions for use’ should be taken into account for the paediatric population.

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Roxavid 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}. This increase is not conisdered clinically relevant.

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}. This increase is not considered clinically relevant.

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 program, numerically higher rates o 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

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A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery
B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years
C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention).

Description of selected adverse reactions
Due to the pharmacological mode of action, the use of Roxavid may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia.

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment.

Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis.

Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock.

In some cases as a consequence of anaemia symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for Roxavid.

Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Paediatric population
Treatment of VTE and prevention of VTE recurrence

The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years. The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

Post-marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of Xarelto. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.

Immune system disorders: Angioedema and allergic oedema
(In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).

Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury)
(In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000)).

Blood and lymphatic system disorders: Thrombocytopenia
(In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/Toxic Epidermal Necrolysis
(In the pooled phase III trials, these events were estimated as very rare (<1/10,000)).

Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia
(In the pooled phase III trials, these events were very rare (< 1/10,000)).

Renal and urinary disorders: Anticoagulant-related nephropathy
(In the pooled phase III trials, the frequency cannot be estimated)

OVERDOSE AND TREATMENT
In adults, rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not 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 agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. 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.

PHARMACODYNAMICS
Pharmacotherapeutic group: 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.

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.

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16 - 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests.

Paediatric population
PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L. The lower limit of quantification must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety of rivaroxaban has been established.

PHARMACOKINETICS
Absorption

the following information is based on the data obtained in adults.
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 and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 2.5mg 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 Roxavid 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.

Paediatric population
Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food.

Distribution
Plasma protein binding in adults 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.

Paediatric population
No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. Vss estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113L for a subject with a body weight of 82.8kg.

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 rivaroxaban 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

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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.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives ($t_{1/2}$) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2–12 years down to 1.9 and 1.6 h in children aged 0.5–<2 years and less than 0.5 years, respectively.
Special populations
Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.
An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children.

Elderly population
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

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

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

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

Hepatic impairment
Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers. Unbound AUC was increased 2.6-fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C.

No clinical data is available in children with hepatic impairment.

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

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Roxavid is to be used with caution in patients with creatinine clearance 15 - 29 ml/min.

No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50mL/min/1.73 m^2).

Pharmacokinetic data in patients
In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) ng/ml, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 12.

Time Intervals								
o.d.	**N**	**12 -< 18 years**	**N**	**6 -< 12 years**				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d	**N**	**6 -< 12 years**	**N**	**2 -< 6 years**	**N**	**0.5 -< 2 years**		
2.5-4h post	36	145.5 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
T.i.d	**N**	**2 -< 6 years**	**N**	**Birth -< 2 years**	**N**	**0.5 -< 2 years**	**N**	**Birth -< 0.5 years**
0.5 - 3h post	5	164.7 (108 - 283)	25	111.2 (22.9 - 320)	13	114.3 (22.9 - 346)	12	108.0 (19.2-320)
7 - 8h post	3	33.2 (18.7 - 99.7)	23	18.7 (10.1 - 36.5)	12	21.4 (10.5 - 65.6)	11	16.1 (1.03 - 33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated.

Values below lower limit of quantification (LLOQ) were substituted by ½ LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

Pharmacokinetic/pharmacodynamic relationship
The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, HepTest) has been evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an Emax model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l).). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

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

Storage:
Do not store above 30°C.
Protect from light & moisture.
Keep out of reach of children.

Presentation/ Packing:
Blister of 4 x 7's Tablets.

Marketing Authorization Holder / Product Registration Holder (Malaysia) / Product Owner:
HOVID Berhad
121, Jalan Tunku Abdul Rahman
(Jalan Kuala Kangsar),
30010 Ipoh, Perak, Malaysia.

Manufactured by:
Inventia Healthcare Limited
F1-F1/1-F75/1, Additional Ambernath M.I.D.C.,
Ambernath (East), Thane,
421506 Maharashtra State, India.

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