SCHEDULING STATUS

S4

WARNING: (A) PREMATURE DISCONTINUATION OF VAROXO INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HAEMATOMA

A. Premature discontinuation of VAROXO increases the risk of thrombotic events:
Premature discontinuation of any oral anticoagulant, including VAROXO, increases the risk of thrombotic events. If anticoagulation with VAROXO is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant (see sections 4.2 and 4.4).

B. Spinal/epidural haematoma:
Epidural or spinal hematomas have occurred in patients treated with VAROXO who are receiving neuraxial anaesthesia or undergoing spinal puncture. These haematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

Factors that can increase the risk of developing epidural or spinal haematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other medicines that affect haemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **History of traumatic or repeated epidural or spinal punctures**
- **History of spinal deformity or spinal surgery**
- **Optimal timing between the administration of VAROXO and neuraxial procedures is not known (see sections 4.8).**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see section 4.4).

1. NAME OF THE MEDICINE

VAROXO 10, 10 mg, film-coated tablets
VAROXO 15, 15 mg, film-coated tablets
VAROXO 20, 20 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VAROXO 10: Each film-coated tablet contains 10 mg rivaroxaban.
VAROXO 15: Each film-coated tablet contains 15 mg rivaroxaban.
VAROXO 20: Each film-coated tablet contains 20 mg rivaroxaban.

Excipients with known effect:
VAROXO 10 contains sugar (lactose monohydrate): 21 mg
VAROXO 15 contains sugar (lactose monohydrate): 31,5 mg
VAROXO 20 contains sugar (lactose monohydrate): 42 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
VAROXO 10: Round, pink, biconvex film-coated tablets debossed with “L” on one side and “10” on the other side.
VAROXO 15: Round, brown, biconvex film-coated tablets debossed with ‘504’ on one side and plain on the other side.
VAROXO 20: Triangle shaped, brown, film-coated tablets debossed with ‘505’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VAROXO 10 is indicated for:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing major orthopaedic surgery of the lower limbs.

VAROXO 15 and VAROXO 20 are indicated for:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF).
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT).

4.2 Posology and method of administration

Posology

VAROXO 10:
During treatment with VAROXO, there is no need for the monitoring of coagulation parameters.
The recommended dose is one VAROXO 10 tablet once daily for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery. The initial dose should be taken within 6 – 10 hours after surgery provided that haemostasis has been established.

Duration of treatment:
The duration of treatment depends on the type of major orthopaedic surgery:

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

Missed dose
If a dose is missed, the patient should take VAROXO 10 immediately and continue on the following day with the once daily intake as before.

Special populations
Patients with hepatic impairment:
Prevention of VTE: VAROXO 10 is contraindicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. (see section 4.3 and 5.2).
No dose adjustment of the 10 mg is necessary in patients with other hepatic diseases.

Patients with renal impairment:
Prevention of VTE: No dose adjustment is required if VAROXO 10 is administered in patients with mild (creatinine clearance 80 to 50 mL/min) or moderate (creatinine clearance < 50 to 30 mL/min) renal impairment.

Paediatric population
The safety and efficacy of VAROXO in children below 18 years have not been established. No data is available.

VAROXO 15 and VAROXO 20:
Posology
There is no need for monitoring of coagulation parameters during treatment with VAROXO 15 and VAROXO 20.

SPAF (Systemic embolism in patients with non-valvular atrial fibrillation)
The recommended dose is one VAROXO 20 tablet once daily, which is also the recommended maximum dose.
For patients with moderate renal impairment (creatinine clearance < 50 to 30 mL/min) the recommended dose is one VAROXO 15 tablet once daily.

SPAF – Duration of treatment:
Therapy should be continued as long as risk factors for stroke and systemic embolism persist.

SPAF – Missed dose:
If a dose is missed, the patient should take VAROXO 15 or VAROXO 20 immediately and continue with the once daily intake as recommended on the following day. The dose should not be doubled to make up for a missed dose within the same day.

SPAF – Maximum daily dose:
The recommended maximum daily dose is one VAROXO 20 tablet (20 mg rivaroxaban).

SPAF

Special populations:

SPAF – Patients with hepatic impairment:

VAROXO 15 and VAROXO 20 are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data is available for patients with severe hepatic impairment (Child Pugh C) (see section 4.3 and 5.2).

SPAF – Patients with renal impairment:

No dose adjustment is required if VAROXO 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 mL/min) renal impairment.

For patients with moderate renal impairment (creatinine clearance < 50 to 30 mL/min) the recommended dose is one VAROXO 15 tablet once daily.

In patients with severe renal impairment (creatinine clearance < 30 to 15 mL/min), rivaroxaban plasma levels are significantly increased. Therefore VAROXO 15 must be used with caution in these patients.

Use of VAROXO is not recommended in patients with creatinine clearance < 15 mL/min (see section 4.4 and 5.2).

SPAF – Converting from warfarin to VAROXO 15 or VAROXO 20:

Warfarin treatment should be stopped and VAROXO 15 or VAROXO 20 therapy should be initiated when the International Normalized Ratio (INR) is ≤ 3,0.

When converting patients from warfarin to VAROXO 15 or VAROXO 20, INR values will be falsely elevated after the intake of VAROXO 15 or VAROXO 20. The INR is not valid to measure the anticoagulant activity of VAROXO 15 or VAROXO 20, and therefore should not be used (see section 4.5).

SPAF – Converting from VAROXO 15 or VAROXO 20 to warfarin:

There is a potential for inadequate anticoagulation during the transition from VAROXO 15 or VAROXO 20 to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that VAROXO 15 and VAROXO 20 can contribute to an elevated INR. In patients converting from rivaroxaban to warfarin, warfarin should be given concurrently until the INR is ≥ 2,0.

For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing, as guided by INR testing. While patients are on both rivaroxaban and warfarin the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban. Once VAROXO is discontinued, INR testing may be done reliably at least 24 hours after the last dose.

SPAF – Converting from parenteral anticoagulants to VAROXO 15 or VAROXO 20:
For patients currently receiving a parenteral anticoagulant, start VAROXO 15 or VAROXO 20, 0 to 2 hours before the time that the next scheduled administration of the parenteral medicine (e.g. low molecular weight heparins - LMWH) or at the time of discontinuation, of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

SPAF – Converting from VAROXO 15 or VAROXO 20 to parenteral anticoagulants:
Discontinue VAROXO 15 or VAROXO 20 and give the first dose of parenteral anticoagulant at the time that the next VAROXO 15 or VAROXO 20 dose would have been taken.

SPAF – Children and adolescents (from birth to 18 years):
The safety and efficacy have not been established in children and adolescents below 18 years.

SPAF – Body weight:
No dose adjustment is required based on body weight.

DVT and PE treatment – Recommended usual dose and frequency of administration:
The recommended dose for the initial treatment of acute DVT and PE is one VAROXO 15 tablet twice daily for the first three weeks followed by one VAROXO 20 tablet once daily for the continued treatment and the prevention of recurrent DVT and PE.
VAROXO 15 and VAROXO 20 tablets should be taken with food.
DVT and PE treatment – Duration of treatment:
Therapy should be continued as long as the VTE (venous thromboembolism) risk persists.

DVT and PE treatment – Missed dose:
It is essential to adhere to the dosage schedule provided.
If a dose is missed during the VAROXO 15 twice daily treatment phase, the patient should take VAROXO 15 immediately to ensure intake of 30 mg per day. In this case, two VAROXO 15 tablets may be taken at once. The patient should continue with the regular one VAROXO 15 tablet twice daily intake as recommended on the following day.
If a dose is missed during the VAROXO 20 once daily treatment phase the patient should take VAROXO 20 immediately to ensure intake of 20 mg per day. The patient should continue with the regular one VAROXO 20 tablet once daily intake as recommended on the following day.

DVT and PE treatment – Maximum daily dose:
The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment.
In the following treatment phase, the recommended maximum daily dose is 20 mg.

DVT and PE treatment
Special populations
DVT and PE treatment – Patients with hepatic impairment:
VAROXO 15 and VAROXO 20 are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3). Limited clinical data in patients with moderate hepatic impairment' (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data is available for patients with severe hepatic impairment (Child Pugh C) (see section 4.3 and 5.2).

DVT and PE treatment – Patients with renal impairment:
No dose adjustment is required if VAROXO 15 and VAROXO 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 mL/min) or moderate (creatinine clearance< 50 to 30 mL/min) renal impairment (see section 5.2).
Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to 15 mL/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore VAROXO 15 and VAROXO 20 must be used with caution in these patients.
Use of VAROXO 15 and VAROXO 20 is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.3 and 5.2).

DVT and PE treatment – Converting from warfarin to VAROXO 15
Warfarin treatment should be stopped and VAROXO 15 therapy should be initiated once the INR is ≤ 2,5.
When converting patients from warfarin to VAROXO 15, INR values will be falsely elevated after the intake of VAROXO 15. The INR is not valid to measure the anticoagulant activity of VAROXO 15, and therefore should not be used (see section 4.5)

DVT and PE treatment – Converting from VAROXO 15 or VAROXO 20 to warfarin:
There is a potential for inadequate anticoagulation during the transition from VAROXO 15 or VAROXO 20 to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that VAROXO 15 or VAROXO 20 can contribute to an elevated INR.
In patients converting from VAROXO 15 or VAROXO 20 to warfarin; warfarin should be given concurrently until the INR is ≥ 2,0. For the first two days of the conversion-period standard warfarin dosing should be used followed by warfarin dosing guided by INR testing. While patients are on both VAROXO 15 or VAROXO 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of VAROXO 15 or VAROXO 20). Once VAROXO 15 or VAROXO 20 is discontinued, INR testing may be done reliably 24 hours after the last dose (see section 4.5).

DVT and PE treatment - Converting from parenteral anticoagulants to VAROXO 15:
For patients currently receiving a parenteral anticoagulant, start VAROXO 15, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

DVT and PE treatment – Converting from VAROXO 15 or VAROXO 20 to parenteral anticoagulants:
Discontinue VAROXO 15 or VAROXO 20 and give the first dose of parenteral anticoagulant at the time that the next VAROXO 15 or VAROXO 20 dose would have been taken.

DVT and PE treatment – Children and adolescents (from birth to 18 years):
Safety and efficacy have not been established in children and adolescents below 18 years.

DVT and PE treatment - Body weight
No dose adjustment is required based on body weight (see section 5.2).

Elderly (above 65 years)
No dose adjustment is required for these patient populations.

Paediatric population
The safety and efficacy of VAROXO in children below 18 years have not been established. No data is available.

Method of administration
The film-coated tablets are for oral use.
VAROXO 15 and VAROXO 20 should be taken with food.
VAROXO 10 can be taken with or without food.

4.3 Contraindications
VAROXO is contraindicated in patients with:
- Hypersensitivity to rivaroxaban or any of the excipients of VAROXO listed in section 6.1.
- Clinically significant active bleeding. (e.g. intracranial bleeding, gastro bleeding)
- Known existing inherited bleeding disorders.
- Hepatic disease with or without coagulopathy, and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Pregnancy and lactation (see section 4.6).
- Persistent triple positive antiphospholipid syndrome (APS).
- 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.

4.4 Special warnings and precautions for use

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

Haemorrhagic risk

As with other anticoagulants, patients taking VAROXO are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Administration of VAROXO should be discontinued if severe haemorrhage occurs (see sections 4.3 and 4.9).

Mucosal bleedings (i.e., epistaxis, gingival, gastrointestinal, genitourinary including abnormal vaginal or increased menstrual bleeding) and anaemia were reported more frequently during long term VAROXO treatment compared with vitamin K antagonist 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 are at increased risk of bleeding (see section 4.8). These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment. In patients receiving VAROXO for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

In addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding.

Although treatment with VAROXO 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

DVT and PE treatment - Renal impairment

VAROXO should be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 mL/min) concomitantly receiving other medicines which increase rivaroxaban plasma concentrations (see section 4.5).

SPAF, DVT and PE treatment - Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 mL/min), rivaroxaban plasma levels may be significantly increased (1,6-fold on average) which may lead to an increased bleeding risk. VAROXO should be used with caution in patients with creatinine clearance 15 to 29 mL/min. Use is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.2 and 5.2).

No dose adjustment is necessary in patients with mild (creatinine clearance 50 to 80 mL/min) or moderate (creatinine clearance < 50 to 30 mL/min) renal impairment.

No clinical data is available for patients with severe renal impairment (creatinine clearance <15 mL/min). Therefore, the use of VAROXO is not recommended in these patients (see sections 4.2, 5.1 and 5.2).

Patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors are to be carefully monitored for signs of bleeding complications after initiation of treatment.

Concomitant medication

VAROXO is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These medicines are strong inhibitors of both CYP3A4 and P-gp. Therefore, these medicines may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see sections 4.5).

The azole anti-mycotic fluconazole, a moderate CYP 3A4 inhibitor, has however, less effect on rivaroxaban exposure and can be co-administered (see sections 4.5).

Care is to be taken if patients are treated concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory medicines (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 (see sections 4.5).

Other haemorrhagic risk factors

VAROXO should be used with caution in patients with an increased bleeding risk such as:

- Congenital or acquired bleeding disorders
- Uncontrolled severe arterial hypertension
- Active ulcerative gastrointestinal disease
- Other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. Inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- Recent gastrointestinal ulcerations
- Vascular retinopathy
- Recent intracranial or intracerebral haemorrhage
- Intraspinal or intracerebral vascular abnormalities
- Shortly after brain, spinal or ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

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 tumour location, antineoplastic therapy and stage of disease.

Patients with prosthetic valves

VAROXO should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR).

Safety and efficacy of VAROXO have not been studied in patients with prosthetic heart valves. There is therefore, no data to support that VAROXO provides adequate anticoagulation in this patient population. Treatment with VAROXO is not recommended for these patients.

Neuraxial (epidural/spinal) anaesthesia

When neuraxial (epidural/spinal) anaesthesia or spinal puncture is performed, patients treated with antithrombotic medicines for prevention of thromboembolic complications are at risk for development of an epidural or spinal haematoma, which may result in long-term paralysis.

The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicines 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 medical practitioner should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg or 20 mg rivaroxaban in these situations.

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

At least 18 hours and 26 hours in elderly patients should elapse after the last administration of rivaroxaban, as in VAROXO, before removal of an epidural catheter. VAROXO should be administered at least 6 hours after the removal of the catheter, or when the anticoagulant effect of VAROXO is estimated to be low.

If a traumatic puncture occurs, the administration of VAROXO should be delayed for 24 hours.

Women of childbearing potential

VAROXO should be used in women of childbearing potential only with effective contraception.

QTc prolongation:

No QTc prolonging effect is observed with VAROXO.

Patient with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including VAROXO are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery

VAROXO has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Patient with non-valvular atrial fibrillation who undergo PCI with stent placement
Evaluation of rivaroxaban as in VAROXO was performed in 7750 patients with non-valvular atrial fibrillation from two phase III trials with at least one dose of VAROXO 15 or VAROXO 20.
Due to the pharmacological mode of action, VAROXO 15 and VAROXO 20 may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in post-haemorrhagic anaemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension, impaired renal and hepatic function and/or on concomitant medication affecting haemostasis. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia.
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.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
VAROXO 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 VAROXO have not been established in these clinical situations.

Elderly population
Increasing age may increase haemorrhagic risk (see section 5.2).

Dermatological reactions
Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first weeks of treatment. VAROXO 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.

QTc prolongation
No QTc prolonging effect was observed with VAROXO

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VAROXO.

4.5 Interaction with other medicines and other forms of interaction
Pharmacokinetic interactions:
Rivaroxaban, as in VAROXO, is cleared mainly via cytochrome P450 mediated (CYP 3A4, CYP 2J2 and CYP-independent mechanisms) hepatic metabolism and renal excretion of the unchanged

medicine, involving the P-glycoprotein (P-gp)/breast cancer resistance protein (Bcrp) transporter systems (see section 5.2).

CYP inhibition:

Rivaroxaban does not inhibit CYP3A4 or any other major CYP isoforms.

CYP induction:

Rivaroxaban does not induce CYP3A4 or any other major CYP isoforms.

Effects on VAROXO:

The concomitant use of VAROXO with strong CYP3A4 and P-gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure.

Co-administration of VAROXO with the azole-antimycotic, ketoconazole (400 mg once daily) or ritonavir, strong CYP3A4 and P-gp inhibitors, can have a 2,6-fold/2,5-fold increase in mean rivaroxaban, as in VAROXO, steady state AUC and a 1,7-fold/1,6-fold increase in mean rivaroxaban C_{max} with significant increases in its pharmacodynamic effects (which may lead to an increased bleeding risk) (see section 4.4).

Therefore, the use of VAROXO is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These medicines are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Co-administration of VAROXO with the HIV protease inhibitor ritonavir (600 mg twice daily), a strong CYP 3A4 and P-gp inhibitor, led to a 2,5 fold increase in mean rivaroxaban AUC and a 1,6 fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk (see section 4.4). Data on the co-administration of VAROXO with the HIV protease inhibitor ritonavir (100 mg twice daily) is not available.

Medicines that strongly inhibit only one of the rivaroxaban, as in VAROXO, elimination pathways, either CYP3A4 or P-gp, are expected to increase its
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, can have (up to a) 1,5-fold increase in mean rivaroxaban, as in VAROXO, AUC and a 1,4-fold increase in C_{max}. This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, can have a 1,3-fold increase in mean rivaroxaban, as in VAROXO, AUC and C_{max}. This increase is not considered clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1,8 fold increase in mean rivaroxaban AUC and 1,6 fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2,0 fold increase in mean rivaroxaban AUC and 1,6 fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, may have a 1,4-fold increase in mean rivaroxaban, as in VAROXO, AUC and a 1,3-fold increase in mean C_{max}. This increase is not considered clinically relevant. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Co-administration of VAROXO with the strong CYP 3A4 and P-gp inducer rifampicin could lead to a 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (see section 5.2).
The concomitant use of VAROXO with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to a decreased rivaroxaban, as in VAROXO, plasma concentration. Strong CYP3A4 inducers should be co-administered with caution or avoided, unless the patient is closely observed for signs and symptoms of thrombosis.
Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Pharmacodynamic interactions:
Anticoagulants
Administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) may have an additive effect on anti-factor Xa activity without any additional effects on clotting tests (PT, aPTT). Enoxaparin will not have any effect on 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
Clopidogrel will not have pharmacokinetic interaction with rivaroxaban, as in VAROXO but a relevant increase in bleeding time may be observed (not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels (see section 4.4).
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicines typically increase the bleeding risk.
No clinically relevant prolongation of bleeding time was observed after concomitant administration of VAROXO 15 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, as in VAROXO, was co-administered with
500 mg acetylsalicylic acid.

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 with VAROXO,
numerically higher rates of major or non-major clinically relevant bleeding were
observed in all treatment groups during clinical studies.

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2,0 to 3,0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg), as in VAROXO, to warfarin (INR 2,0 to 3,0) will have an increase in the 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 needed to test the pharmacodynamic effects of rivaroxaban, as in VAROXO, during the conversion period, anti-factor Xa activity, prothrombinase-induced clotting time (PiCT), and Heptest® can be used as these tests are 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) will reflect only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban, as in VAROXO.

CYP3A4 inducers
Co-administration of VAROXO 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 VAROXO 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.

No interactions:
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban, as in VAROXO, was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP3A4 and P-gp). Rivaroxaban, as in VAROXO, neither inhibits nor induces any major CYP isoforms like CYP3A4.
Co-administration of the proton pump inhibitor, omeprazole, H2 receptor antagonist, ranitidine, the antacid, aluminium hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin, will not affect the bioavailability and pharmacokinetics of rivaroxaban, as in VAROXO.

Interaction with laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) will be affected (as expected) by the mode of action of rivaroxaban.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential
Women of child-bearing potential should avoid becoming pregnant or use effective contraception during treatment with VAROXO. (see section 4.4)

Pregnancy
The use of VAROXO is contraindicated in pregnancy. (see section 4.3)
Safety and efficacy of rivaroxaban have not been established in pregnant women. In rats and rabbits, rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g. haemorrhagic complications), leading to reproductive toxicity.
It has been shown that VAROXO crosses the placenta and may cause an intrinsic risk of bleeding.

Lactation
Safety and efficacy of VAROXO have not been established in lactating mothers. VAROXO may only be administered after breastfeeding is discontinued (see section 4.3).

Fertility:
No data available.

4.7 Effects on the ability to drive and use machines
VAROXO has minor influence on the ability to drive and use machines. Syncope and dizziness may be experienced. It is, therefore, recommended that patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects
a. Summary of the safety profile
There may be an increased risk of occult or overt bleeding from any tissue and organ which may result in post haemorrhagic anaemia due to the pharmacological mode of action of VAROXO. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension, impaired renal and hepatic function and/or on concomitant medication affecting haemostasis (see section 4.4). The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock.
Symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed in some cases as a consequence of anaemia.
Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for VAROXO. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	*Frequent*	Anaemia (including respective laboratory parameters).
	Less frequent	Thrombocythemia (incl. platelet count increased) [A], thrombocytopenia
Immune system disorders	*Less frequent*	Allergic reaction, allergic dermatitis, angioedema, allergic oedema and anaphylactic reactions including anaphylactic shock
Nervous system disorders	*Frequent*	Dizziness and headache.
	Less frequent	Cerebral and intracranial haemorrhage, syncope.
Eye disorders	*Frequent*	Eye haemorrhage (incl. conjunctival haemorrhage).
Cardiac disorders	*Less frequent*	Tachycardia

Vascular disorders	*Frequent*	Hypotension and haematoma
Respiratory, thoracic and mediastinal disorders	*Frequent*	Epistaxis, haemoptysis
Gastrointestinal disorders	*Frequent*	Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation [A], diarrhoea, vomiting [A]
	Less frequent	Dry mouth
Hepato-biliary disorders	*Frequent*	Increase in transaminases
	Less frequent	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase [A], increased GGT [A], jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)
Skin and subcutaneous tissue disorders	*Frequent*	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage
	Less frequent	Urticaria, Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis, DRESS syndrome
Musculoskeletal and connective tissue disorders	*Frequent*	Pain in extremity [A]
	Less frequent	Haemarthrosis, muscle haemorrhage
	Unknown frequency	Compartment syndrome secondary to a bleeding
Renal and urinary disorders	*Frequent*	Urogenital tract haemorrhage (incl. haematuria and menorrhagia [B]), renal impairment (incl. blood creatinine increased, blood urea increased)
	Frequency unknown	Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions	*Frequent*	Fever [A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)
	Less frequent	Feeling unwell (incl. malaise), localised oedema [A]
Investigations	*Frequent*	Increase in transaminase (incl. ALT increase, AST increase).
	Less frequent	Increased LDH [A], increased lipase [A], increased amylase [A] Increase in GGT [A],

Injury, poisoning and procedural complications	*Frequent*	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion [A]
	Less frequent	Vascular pseudoaneurysm [C]

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

c. Description of selected adverse reactions

Due to the pharmacological mode of action, the use of VAROXO 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 (see section 4.9 “Management of bleeding”). Mucosal bleedings (i.e., epistaxis, gingival, gastrointestinal, genitourinary including abnormal vaginal or increased menstrual bleeding) and anaemia have been reported more frequently during long term VAROXO treatment compared with vitamin K antagonist 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, impaired renal and hepatic function and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). 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 VAROXO. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the VAROXO is important. It allows continued monitoring of the benefit/risk balance of the VAROXO. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
Overdose following administration of VAROXO may lead to haemorrhagic complications due to its pharmacodynamic properties. The use of activated charcoal to reduce absorption in case of VAROXO

overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban.
Due to the high plasma protein binding, VAROXO is not expected to be dialysable.

Should bleeding occur, management of the haemorrhage may include the following steps:

- Delay of the next VAROXO administration or discontinuation of treatment as appropriate. Rivaroxaban, as in VAROXO, has a half-life of approximately 5 to 13 hours (see section 5.2).
- Appropriate symptomatic treatment, e.g. mechanical compression (e.g., for severe epistaxis), surgical interventions, fluid replacement and haemodynamic support, blood product (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- Specific factor Xa inhibitor reversal agent (and exanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, as in VAROXO
- Activated prothrombin complex concentrate (APCC)
- Prothrombin complex concentrate (PCC)
- Recombinant Factor VIIa (rF VIIa)

However, there is currently very limited clinical experience with the use of these medicines in individuals receiving rivaroxaban, as in VAROXO.
Protamine Sulphate and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban as in VAROXO. There is no experience with antifibrinolytic medicines (tranexamic acid, aminocaproic acid) in individuals receiving VAROXO. There is neither scientific rationale for benefit nor experience with the system haemostatics desmopressin and aprotinin in individuals receiving VAROXO.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic medicines, direct factor Xa inhibitors, ATC code: B01AF01
Pharmacological classification: A.8.2

Mechanism of action:
Rivaroxaban is a highly selective inhibitor of the direct factor Xa with oral bioavailability.
The activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa converts prothrombin directly to thrombin through the prothrombinase complex, a reaction which leads to fibrin clot formation and the activation of platelets by thrombin.
More than 1 000 molecules of thrombin can be generated from just one molecule of FXa due to the amplification nature of the coagulation cascade. Additionally, the reaction rate of prothrombinase-bound FXa increases 300 000-fold compared to that of free FXa and causes an explosive burst of thrombin generation.
The amplified burst of thrombin generation can be terminated by selective inhibitors of FXa. Consequently, several specific and global clotting tests are affected by rivaroxaban.
Dose dependent inhibition of factor Xa activity was observed in humans.

Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects

Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way. 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 the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and for the prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 seconds for the 10 mg, 17 seconds to 32 seconds for 15 mg twice daily or 15 seconds to 30 seconds for 20 mg once daily, respectively.

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 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 14 seconds to 40 seconds in patients treated with 20 mg once daily and from 10 seconds to 50 seconds in patients with moderate renal impairment treated with 15 mg once daily.

The activated partial thomboplastin time (aPTT) and HepTest® are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. Anti-factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available.

5.2 Pharmacokinetic properties

Absorption

Rivaroxaban is rapidly absorbed achieving maximum concentrations (C_{max}) 2 – 4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 – 100 %) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food has been shown to have no effect on rivaroxaban AUC or C_{max} at the 10 mg dose.

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with interindividual variability (CV %) ranging from 30 % to 40 %, apart from on the day of surgery and the following day when variability in exposure is high (70 %).

Distribution

Plasma protein binding is high in humans, at approximately 92 % to 95 % with serum albumin being the main binding component. The volume of distribution is moderate, with V_{ss} (steady-state volume of distribution) being approximately 50 litres.

Metabolism and elimination

Approximately 2/3 of the administered rivaroxaban dose undergoes metabolic degradation, with half eliminated renally and the other half eliminated by the faecal route. The other 1/3 of the administered

dose undergoes direct renal excretion (mainly via active renal secretion) as unchanged active substance in the urine.
Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 and CYP-independent mechanisms. The major sites of biotransformation are oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds. Based on *in vitro* investigations, rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).
The most important compound in human plasma is the unchanged rivaroxaban, with no major or active circulating metabolites being present. Rivaroxaban can be classified as a low-clearance substance as it has a systemic clearance of about 10 L/h. In young individuals, elimination of rivaroxaban from plasma occurred with terminal half-life of 5 to 9 hours, and with terminal half-life of 11 to 13 hours in the elderly.

Linearity/Non-linearity
Rivaroxaban pharmacokinetics is linear with no relevant undue accumulation beyond steady-state after multiple doses.

Pharmacokinetics in Special populations
Elderly patients
Elderly patients may show higher plasma concentrations than younger patients, with mean AUC values being approximately 1,5-fold higher, mainly due to reduction in (apparent) total and renal clearance. No dose adjustment is necessary (see section 4.2).

Gender
No clinically significant differences can be expected in the pharmacokinetics and pharmacodynamics between male and female patients.

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

Children and adolescents
Safety and efficacy have not been established for children and adolescents below 18 years.

Inter-ethnic differences
No clinically relevant inter-ethnic differences were observed regarding pharmacokinetics and pharmacodynamics.

Hepatic impairment
The effect of hepatic impairment on rivaroxaban pharmacokinetics has been researched in patients categorised according to the Child Pugh classification, a standard procedure in clinical development. In patients for whom anticoagulation is intended, the critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver. Since this aspect is captured by only one of the

five clinical/biochemical measurements composing the Child Pugh classification system, the bleeding risk in patients may not clearly correlate with this classification scheme.
Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) may show minor changes in rivaroxaban pharmacokinetics (a 1,2-fold increase in rivaroxaban AUC on average). In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC may (significantly) increase by 2,3-fold. Unbound AUC may increase 2,6-fold. The changes in AUC may also be due to a reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There is no data in patients with severe hepatic impairment.
The inhibition of factor Xa activity may show an increase by a factor of 2,6 in patients with moderate hepatic impairment; prolongation of PT may similarly be increased by a factor of 2,1. The global clotting test PT assesses the extrinsic pathway that comprises of the coagulation factors VII, X, V, II, I which are synthesised in the liver. Patients with moderate hepatic impairment may be more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
No data is available for Child Pugh C patients (see section 4.2 and 4.3).
Rivaroxaban is contraindicated in patients with hepatic disease associated with or without coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment
A decreased renal function correlated to an increase in rivaroxaban exposure, as assessed via creatinine clearance measurements.
In individuals with mild (creatinine clearance ≤ 80 to 50 mL/min), moderate (creatinine clearance < 50 to 30 mL/min) or severe (creatinine clearance < 30 to 15 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) can be expected to increase 1,4; 1,5 and 1,6-fold respectively.
Corresponding increases in pharmacodynamic effects are more pronounced (see section 4.4 and section 4.2).
In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity could increase by a factor of 1,5; 1,9 and 2,0 respectively; prolongation of PT may similarly increase by a factor of 1,3; 2,2 and 2,4 respectively. There is no data in patients with creatinine clearance of < 15 mL/min.
In patients with severe renal impairment (with a creatinine clearance of < 30 to 15 mL/min) rivaroxaban is to be used with caution (see section 4.4 and section 4.2). Due to the underlying disease, patients with severe renal impairment are at an increased risk of both thrombosis and bleeding.

Concomitant administration of strong CYP 3A4 inducers
Co-administration of rivaroxaban with rifampicin (a strong CYP3A4 and P-gp inducer) may lead to a 50 % decrease in the mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (see section 4.5).

Paediatric population
Safety and efficacy have not been established for children and adolescents below 18 years (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Croscarmellose Sodium
Microcrystalline cellulose
Hypromellose
Sodium lauryl sulfate
Colloidal silicon dioxide
Magnesium stearate (vegetable source)

Tablet coating

10 mg - Opadry Pink

Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide red (E172)

15 mg and 20 mg - Opadry Brown

Hypromellose
Titanium dioxide (E171)
Macrogol
Iron oxide red (E172)
Ferrosoferric oxide / black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C.
Keep blisters in outer carton until required for use.

6.5 Nature and contents of container

Blister of plain aluminium lidding foil and transparent PVC / PVdC film containing 10 or 14 film-coated tablets.
Pack sizes:
10 mg: cartons containing 10, 30 or 100 tablets
15 mg: cartons containing 10, 30, 40, 42 or 100 tablets
20 mg: cartons containing 10, 28, 30, 40 or 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER (S)

VAROXO 10: 53/8.2/0272
VAROXO 15: 53/8.2/0273
VAROXO 20: 53/8.2/0274

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 August 2022

10. DATE OF REVISION OF THE TEXT

26 March 2025