PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

RIVOXA® 10 (film-coated tablets)

RIVOXA® 15 (film-coated tablets)

RIVOXA® 20 (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIVOXA 10: Each film-coated tablet contains 10 mg rivaroxaban.

RIVOXA 15: Each film-coated tablet contains 15 mg rivaroxaban.

RIVOXA 20: Each film-coated tablet contains 20 mg rivaroxaban.

Excipient with known effect:

RIVOXA 10: Each film-coated tablet contains 28,09 mg lactose (as monohydrate).

RIVOXA 15: Each film-coated tablet contains 21,068 lactose (as monohydrate).

RIVOXA 20: Each film-coated tablet contains 28,09 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet *(tablet)*

RIVOXA 10: Light-red, round, biconvex, film-coated tablet, debossed with “C5” on one side, plain on the other side.

RIVOXA 15: Red, round, biconvex, film-coated tablet, debossed with “C4” on one side, plain on the other side.

RIVOXA 20: Brown-red, round, biconvex, film-coated tablet, debossed with “C3” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

RIVOXA 10 mg is indicated for:

The prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

RIVOXA 15 mg and 20 mg 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

Recommended dose and frequency of administration for RIVOXA 10:

The recommended dose is one RIVOXA 10 tablet once daily for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery.

RIVOXA 10 may be taken with or without food.

The initial dose should be taken within 6 to 10 hours after surgery provided that haemostasis has been established.

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

Duration of treatment:

The duration of treatment depends on the type of major orthopaedic surgery.

After major hip surgery patients should be treated for 5 weeks.

After major knee surgery patients should be treated for 2 weeks.

Special patient populations:

Elderly (above 65 years), gender and body weight:

No dose adjustment is required for these patient populations.

Patients with impaired liver function:

RIVOXA 10 is contraindicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 4.3).

No dose adjustment is necessary in patients with other hepatic diseases.

Limited clinical data in patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment.

Patients with impaired renal function:

No dose adjustment is required if RIVOXA 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.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 mL/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore RIVOXA 10 has to be used with caution in these patients (see section 4.4).

Ethnic differences

No dosage adjustment is required based on ethnic differences.

Paediatric population

The safety and efficacy of RIVOXA 10 has not been established in children. No clinical data is available for children.

Recommended dose and frequency of administration for RIVOXA 15 and RIVOXA 20:

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

SPAF – Recommended usual dose and frequency of administration:

The recommended dose is one RIVOXA 20 tablet once daily.

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

RIVOXA 15 and RIVOXA 20 tablets should be taken with food.

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 RIVOXA 15 or RIVOXA 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 RIVOXA 20 tablet (20 mg rivaroxaban).

SPAF – Additional information on special populations:

SPAF – Patients with hepatic impairment:

RIVOXA 15 and RIVOXA 20 are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3). Limited data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

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

SPAF – Patients with renal impairment:

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

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

Limited 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, RIVOXA 15 has to be used with caution in these patients.

Use of RIVOXA 15 or RIVOXA 20 is not recommended in patients with creatinine clearance < 15 mL/min (see section 4.4 and section 5.2).

SPAF – Converting from warfarin to RIVOXA 15 and RIVOXA 20:

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

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

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

There is a potential for inadequate anticoagulation during the transition from RIVOXA 15 or RIVOXA 20 to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that RIVOXA 15 and RIVOXA 20 can contribute to an elevated INR.

In patients converting from RIVOXA 15 or RIVOXA 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 RIVOXA 15 or RIVOXA 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of RIVOXA 15 or

RIVOXA 20). Once RIVOXA 15 or RIVOXA 20 is discontinued, INR testing may be done reliably 24 hours after the latest dose (see section 4.5).

SPAF – Converting from parenteral anticoagulants to RIVOXA 15 or RIVOXA 20:

For patients currently receiving a parenteral anticoagulant, start RIVOXA 15 or RIVOXA 20, 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).

SPAF – Converting from RIVOXA 15 or RIVOXA 20 to parenteral anticoagulants:

Discontinue RIVOXA 15 or RIVOXA 20 and give the first dose of parenteral anticoagulant at the time that the next RIVOXA 15 or RIVOXA 20 dose would have been taken.

SPAF – Paediatric population (from birth to 18 years):

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 (see section 5.2).

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 RIVOXA 15 tablet **twice daily** for the first three weeks followed by one RIVOXA 20 tablet **once daily** for the continued treatment and the prevention of recurrent DVT and PE.

RIVOXA 15 and RIVOXA 20 tablets should be taken with food.

DVT and PE treatment – Duration of treatment:

Therapy should be continued as long as the VTE 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 RIVOXA 15 twice daily treatment phase the patient should take RIVOXA 15 immediately to ensure an intake of 30 mg per day. The patient should continue with the regular one RIVOXA 15 tablet twice daily intake as recommended on the following day.

If a dose is missed during the RIVOXA 20 once daily treatment phase the patient should take RIVOXA 20 immediately to ensure intake of 20 mg per day. The patient should continue with the regular one RIVOXA 20 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 – Additional information of special populations:

DVT and PE treatment – Patients with hepatic impairment:

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

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

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

DVT and PE treatment – Patients with renal impairment:

No dose adjustment is required if RIVOXA 15 and RIVOXA 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 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 RIVOXA 15 and RIVOXA 20 has to be used with caution in these patients.

Use of RIVOXA 15 and RIVOXA 20 are not recommended in patients with creatinine clearance < 15 mL/min (see section 4.4 and section 5.2).

DVT and PE treatment – Converting from warfarin to RIVOXA 15:

Warfarin treatment should be stopped and RIVOXA 15 therapy should be initiated once the INR is ≤ 2,5.

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

DVT and PE treatment – Converting from RIVOXA 15 and RIVOXA 20 to warfarin:

There is a potential for inadequate anticoagulation during the transition from RIVOXA 15 and RIVOXA 20 to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that RIVOXA 15 and RIVOXA 20 can contribute to an elevated INR.

In patients converting from RIVOXA 15 or RIVOXA 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 RIVOXA 15 or RIVOXA 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of RIVOXA 15 or RIVOXA 20). Once RIVOXA 15 or RIVOXA 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 RIVOXA 15:

For patients currently receiving a parenteral anticoagulant, start RIVOXA 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 RIVOXA 15/20 to parenteral anticoagulants:

Discontinue RIVOXA 15 or RIVOXA 20 and give the first dose of parenteral anticoagulant at the time that the next RIVOXA 15 or RIVOXA 20 dose would have been taken.

DVT and PE treatment – Paediatric population (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).

Method of administration:

Oral use.

4.3 Contraindications:

RIVOXA is contraindicated in patients with:

- Hypersensitivity to rivaroxaban or to any of the excipients of RIVOXA, listed in section 6.1.
- 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 (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 5.2).
- Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use:

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

Haemorrhagic risk:

Patients taking RIVOXA are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. RIVOXA administration should be discontinued if severe haemorrhage occurs.

In clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary 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 (see section 4.8).

In patients receiving RIVOXA 10 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.

Although treatment with RIVOXA 15 and RIVOXA 20 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 (see sections 5.1 and 5.2).

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.

RIVOXA is to 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).

In patients with moderate renal impairment (creatinine clearance 30 to 49 mL/min) concomitantly receiving other medicines which increase rivaroxaban plasma concentrations, RIVOXA is to be used with caution (see section 4.5).

Interaction with other medicines:

The use of RIVOXA 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 (see section 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 (ASA) 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 section 4.5).

Other haemorrhagic risk factors:

Rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding.

Patients with prosthetic valves:

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

Patients with antiphospholipid syndrome:

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

Patients with non-valvular atrial fibrillation who undergo percutaneous coronary intervention (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 (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/TIA.

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

RIVOXA 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 RIVOXA 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 medicines 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 postoperative 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 and 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 (see

section 5.2). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

For the removal of an epidural catheter and based on the general PK characteristics at least 2 x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban (see section 5.2).

Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

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

Dosing recommendations before and after invasive procedures and surgical intervention:

Knee replacement surgery

If an invasive procedure or surgical intervention is required, RIVOXA should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the medical practitioner. If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.

RIVOXA 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 medical practitioner (see section 5.2).

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 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. RIVOXA 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:

RIVOXA contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction:

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 RIVOXA 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 (see section 4.4).

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. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1,3 fold increase in mean rivaroxaban AUC and C_{max}. The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients.

In subjects with mild renal impairment, erythromycin (500 mg three times a day) led to a 1,8 fold increase in mean rivaroxaban AUC and 1,6 fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2,0 fold increase in mean rivaroxaban AUC and 1,6 fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

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

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 (see sections 4.3 and 4.4).

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 medicines typically increase the bleeding risk (see section 4.4).

SSRIs/SNRIs

The possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2,0 to 3,0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2,0 to 3,0) increased prothrombin time/INR (Neoplastin®) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and HepTest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort *(Hypericum perforatum)*) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (see section 5.1).

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Pregnancy:

Safety and efficacy of RIVOXA have not been established in pregnant women.

Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, RIVOXA is contraindicated during pregnancy (see section 4.3).

Breastfeeding:

Safety and efficacy of RIVOXA have not been established in breastfeeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, RIVOXA is contraindicated during breastfeeding (see section 4.3).

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.

4.7 Effects on ability to drive and use machines:

RIVOXA has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects:

Tabulated list of adverse reactions

Blood and lymphatic system disorders:	
Frequent:	Anaemia (incl. respective laboratory parameters).
Less frequent:	Thrombocytosis (incl. platelet count increased - observed in prevention of VTE in adult patients undergoing elective hip or knee replacement), thrombocytopenia (incl. platelet count increased).
Immune system disorders:	
Less frequent:	Allergic reaction, anaphylactic reactions including anaphylactic shock, angioedema and allergic oedema, allergic dermatitis.
Nervous system disorders:	
Frequent:	Dizziness, headache.
Less frequent:	Cerebral and intracranial haemorrhage, syncope (incl. loss of consciousness).
Eye disorders:	
Frequent:	Eye haemorrhage (incl. conjunctival haemorrhage).
Cardiac disorders:	
Less frequent:	Tachycardia.
Vascular disorders:	
Frequent:	Haematoma, hypotension, postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage).
Less frequent:	(See Gastrointestinal disorders), genital tract haemorrhage (incl. menorrhagia), haemorrhage (incl. haematoma and rare cases of muscle haemorrhage), haematuria (incl. blood urine present), nosebleed.

Respiratory, thoracic and mediastinal disorders:

Frequent: Epistaxis, haemoptysis.

Gastrointestinal disorders:

Frequent: Constipation (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement), diarrhoea, dyspepsia (including epigastric discomfort), gastrointestinal and abdominal pains, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gingival bleeding, nausea, vomiting (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement).

Less frequent: Dry mouth.

Hepatobiliary disorders:

Frequent: Increase in transaminases.

Less frequent: Abnormal hepatic function, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatic impairment, hepatitis (incl. hepatocellular injury), increased bilirubin, increased blood alkaline phosphatase (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement), increased GGT (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement), jaundice.

Skin and subcutaneous tissue disorders:

Frequent: Cutaneous and subcutaneous haemorrhage, ecchymosis, pruritus (incl. uncommon cases of generalised pruritus), rash.

Less frequent: Contusion, Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome, urticaria (incl. rare cases of generalised urticaria).

Musculoskeletal and connective tissue disorders:

Frequent: Pain in extremity (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement).

Less frequent: Compartment syndrome secondary to a bleeding, haemarthrosis, muscle haemorrhage.

Renal and urinary disorders:

Frequent: Renal impairment (incl. blood creatinine increased, blood urea increased observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery), urogenital tract haemorrhage (incl. haematuria and menorrhagia observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years).

Less frequent: Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion.

General disorders and administration site conditions:

Frequent: Decreased general strength and energy (incl. fatigue and asthenia), fever (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery), peripheral oedema.

Less frequent: Feeling unwell (incl. malaise), localised oedema (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery).

Investigations:

Frequent: Increase in transaminases (incl. ALT increase, AST increase), increased GGT.

Less frequent:	Bilirubin conjugated increased (with or without concomitant increase of ALT), blood bilirubin increased, increased alkaline phosphatase, increased LDH- lipase- and amylase observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery.
Injury, poisoning and procedural complications:	
Frequent:	Contusion, postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), wound secretion (observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery).
Less frequent:	Vascular pseudoaneurysm - observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention), wound secretion.

Description of selected adverse reactions:

Due to the pharmacological mode of action, the use of RIVOXA 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). In the clinical studies, mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary 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 (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 RIVOXA. 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the 6.04 Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 supra therapeutic doses of 50 mg rivaroxaban or above.

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 (see section 5.2). 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, administration of a specific procoagulant reversal medicine should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is very limited clinical experience with the use of these products in individuals receiving rivaroxaban. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

There is no experience with antifibrinolytic medicines (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Category and class: A 8.2 Anticoagulants

Pharmacotherapeutic group: Antithrombotic medicines, direct factor Xa inhibitors, ATC code: B01AF01.

Mechanism of action:

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability.

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 directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1 000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, 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.
Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of factor Xa activity was observed in humans.

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.

RIVOXA 10:

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 (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT, 2 to 4 hours after tablet intake (i.e. at the time of maximum effect), ranged from 13 to 25 seconds.

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.

Anti-factor Xa activity is also influenced by rivaroxaban; however, no standard for calibration is available.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban.

RIVOXA 15 and 20 mg:

In patients receiving rivaroxaban for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and 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) for 15 mg rivaroxaban twice daily ranged from 17 to 32 seconds and for 20 mg rivaroxaban once daily from 15 to 30 seconds, 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 thromboplastin 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 and bioavailability:

RIVOXA 10:

The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. Rivaroxaban is well absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake. Administration of rivaroxaban tablets with food (high-calorie/high-fat meal) showed no significant food effects. Rivaroxaban 10 mg dose can be taken with or without food (see section 4.2).

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

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.

RIVOXA 15 and RIVOXA 20:

Rivaroxaban is well absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

The oral bioavailability for RIVOXA 20 tablet dose is 66 %, under fasting conditions. When RIVOXA 20 tablets are taken together with food, increases in mean AUC by 39 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. RIVOXA 15 and RIVOXA 20 should be taken with food (see section 4.2).

Under fed conditions RIVOXA 15 and RIVOXA 20 tablets demonstrated dose-proportionality.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.

Distribution

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

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately ⅔ undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The other ⅓ of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. 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.

Special populations:

Gender:

There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

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 (see section 4.2).

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.

Hepatic impairment:

The effect of hepatic impairment on rivaroxaban pharmacokinetics has been studied in subjects 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 five clinical/biochemical measurements composing the Child Pugh classification system, the bleeding risk in patients may not clearly correlate with this classification.

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, due to significantly impaired medicine clearance which indicates significant liver disease. 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.

No data are available for Child Pugh C patients (see sections 4.2 and 4.3). RIVOXA is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Renal impairment:

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 to 80 mL/min), moderate (creatinine clearance 30 to 49 mL/min) and severe (creatinine clearance 15 to 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 (see sections 4.4 and 4.2).

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. Use is not recommended in patients with creatinine clearance < 15 mL/min.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance < 30 to 15 mL/min) (see sections 4.4 and 4.2). Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

Paediatric population:

Safety and efficacy have not been established for children and adolescents up to 18 years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Tablet:

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Hypromellose

Sodium lauryl sulphate

Colloidal anhydrous silica

Magnesium stearate

Film coating:

Hypromellose (E464)

Iron oxide red (E172)

Titanium dioxide (E171)

Macrogol (E1521)

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

36 months

6.4 Special precautions for storage:

Store at or below 25 °C. Keep blister strips in the original carton until use.

6.5 Nature and contents of container:

RIVOXA 10 mg film-coated tablets are available in Alu hard tempered foil – clear film PVC/PVDC blister pack. The blister strips are packed in cartons containing 10, 15 or 30 tablets.

Not all packing sizes may be marketed at one time.

RIVOXA 15 mg film-coated tablets are available in Alu hard tempered foil – clear film PVC/PVDC blister pack. The blister strips are packed in cartons containing 28, 30 or 42 tablets.

Not all packing sizes may be marketed at one time.

RIVOXA 20 mg film-coated tablets are available in Alu hard tempered foil – clear film PVC/PVDC blister pack. The blister strips are packed in cartons containing 28 or 30 tablets.

Not all packing sizes may be marketed at one time.

6.6 Special precautions for disposal and other handling:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

Suite C, Rubenstein Ridge

617 Rubenstein Drive

Moreleta Park, 0181

South Africa

8. REGISTRATION NUMBERS

RIVOXA 10 – 56/8.2/1008

RIVOXA 15 – 56/8.2/1009

RIVOXA 20 – 56/8.2/1010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 28 November 2023

10. DATE OF REVISION OF THE TEXT

Not applicable