SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

REXARAV 15 mg Film-coated tablets

REXARAV 20 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: lactose monohydrate 30,375 mg per tablet.

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

Contains sugar: lactose monohydrate 40,500 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

REXARAV 15 mg: A pink to brick red coloured, film-coated, round, biconvex, beveled edge tablet, debossed with RX on one side of the tablet and 3 on the other side. Diameter: Approximately 6,4 mm ± 0,5 mm

REXARAV 20 mg: A light pink to pink coloured, film-coated, round, biconvex, bevelled edge tablet, debossed with RX on one side of the tablet and 4 on the other side. Diameter: Approximately 7,0 mm ± 0,5 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

REXARAV 15 mg and REXARAV 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

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

SPAF - Recommended usual dose and frequency of administration:

The recommended dose is one REXARAV 20 mg tablet once daily.

For patients with moderate renal impairment (creatinine clearance < 50 to 30 mL/min) the recommended dose is one REXARAV 15 mg 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 REXARAV 15 mg or RIVAROXABAN 20 mg 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 REXARAV 20 mg tablet (20 mg rivaroxaban).

SPAF - Additional information on special populations:

SPAF - Patients with hepatic impairment:

REXARAV 15 mg and REXARAV 20 mg 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 are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

SPAF - Patients with renal impairment:

No dose adjustment is required if REXARAV 20 mg 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 REXARAV 15 mg once daily.

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 REXARAV 15 mg must be used with caution in these patients.

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

SPAF - Converting from warfarin to REXARAV 15 mg or REXARAV 20 mg:

Warfarin treatment should be stopped and REXARAV 15 mg or REXARAV 20 mg therapy should be initiated when the INR is ≤ 3,0.

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

SPAF - Converting from REXARAV 15 mg or REXARAV 20 mg to warfarin:

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

In patients converting from REXARAV 15 mg or REXARAV 20 mg 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 REXARAV 15 mg or REXARAV 20 mg and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of REXARAV 15 mg or REXARAV 20 mg). Once REXARAV 15 mg or REXARAV 20 mg is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF - Converting from parenteral anticoagulants to REXARAV 15 mg or REXARAV 20 mg:

For patients currently receiving a parenteral anticoagulant, start REXARAV 15 mg or REXARAV 20 mg, 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 REXARAV 15 mg or REXARAV 20 mg to parenteral anticoagulants:

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

SPAF - Children and adolescents (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 REXARAV 15 mg tablet twice daily for the first three weeks followed by one REXARAV 20 mg tablet once daily for the continued treatment and the prevention of recurrent DVT and PE.

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 REXARAV 15 mg twice daily treatment phase the patient should take REXARAV 15 mg immediately to ensure intake of 30 mg per day. In this case two REXARAV 15 mg tablets may be taken at once. The patient should continue with the regular one REXARAV 15 mg twice daily intake as recommended on the following day.

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

DVT and PE treatment - Patients with hepatic impairment:

REXARAV 15 mg and REXARAV 20 mg 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 are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

DVT and PE treatment - Patients with renal impairment:

No dose adjustment is required if REXARAV 15 mg and REXARAV 20 mg 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 REXARAV 15 mg and REXARAV 20 mg must be used with caution in these patients.

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

DVT and PE treatment - Converting from warfarin to REXARAV 15 mg:

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

When converting patients from warfarin to REXARAV 15 mg, INR values will be falsely elevated after the intake of REXARAV 15 mg. The INR is not valid to

measure the anticoagulant activity of REXARAV 15 mg, and therefore should not be used (see section 4.5).

DVT and PE treatment - Converting from REXARAV 15 mg or REXARAV 20 mg to warfarin:

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

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

For patients currently receiving a parenteral anticoagulant, start REXARAV 15 mg, 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 REXARAV 15 mg or REXARAV 20 mg to parenteral anticoagulants:

Discontinue REXARAV 15 mg or REXARAV 20 mg and give the first dose of parenteral anticoagulant at the time that the next REXARAV 15 mg or REXARAV

20 mg dose would have been taken.

DVT and PE treatment - Body weight:

No dose adjustment is required based on body weight (see section 5.2).

Paediatric population

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.

Method of administration:

Oral use.

REXARAV 15 mg and REXARAV 20 mg tablets should be taken with food.

4.3 Contraindications

- Hypersensitivity to rivaroxaban or to any of the excipients of REXARAV (see section 6.1).
- Active clinically significant bleeding (e.g. intracranial bleeding, gastrointestinal 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 lactation (see section 4.6).
- Patients with persistent triple positive antiphospholipid syndrome (APS).

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 REXARAV must be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. REXARAV administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term REXARAV treatment compared with vitamin K antagonist (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). Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with REXARAV 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. REXARAV is to be used with caution in patients with creatinine clearance 15 - 29 mL/min. Use is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.2 and 5.2).

REXARAV should be used with caution in patients with renal impairment concomitantly receiving other medicines which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicines

The use of REXARAV 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 nonsteroidal 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 section 4.5).

Other haemorrhagic risk factors

REXARAV 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
- recent intracranial or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- shortly after brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

Patients with prosthetic valves

REXARAV should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of REXARAV have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that REXARAV provides adequate

anticoagulation in this patient population. Treatment with REXARAV is not recommended for these patients.

Patients with antiphospholipid syndrome (APS)

Direct acting Oral Anticoagulants (DOACs) including REXARAV 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 (see section 4.3).

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with nonvalvular 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

REXARAV 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 REXARAV have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is performed, 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 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 20 mg rivaroxaban in these situations.

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

For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of REXARAV (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next REXARAV dose is administered. If traumatic puncture occurs the administration of REXARAV is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, REXARAV 20 mg should be stopped at least 24 hours before the intervention. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention. REXARAV 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. REXARAV 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.

Excipients

REXARAV contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, total lactase

deficiency or glucose-galactose malabsorption should not take REXARAV.

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 REXARAV 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 REXARAV 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 child-bearing potential should avoid becoming pregnant during treatment with REXARAV.

Pregnancy

Safety and efficacy of REXARAV 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, REXARAV is contraindicated during pregnancy (see section 4.3).

Breastfeeding

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

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility.

4.7 Effects on ability to drive and use machines

REXARAV 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

a. Summary of the safety profile

The safety of rivaroxaban has been evaluated in four phase III studies including 6097 patients exposed to rivaroxaban 10 mg undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) in 3997 hospitalised medically ill patients treated up to 39 days, and in three phase III VTE treatment trials with 4556 patients exposed either to rivaroxaban 15 mg twice daily for 3 weeks followed by rivaroxaban 20 mg once daily or to rivaroxaban 20 mg once daily treated up to 21 months

Furthermore, safety of rivaroxaban has also been evaluated in 7750 patients with non-valvular atrial fibrillation from two phase III trials with at least one dose of rivaroxaban 15 mg or rivaroxaban 20 mg.

Due to the pharmacological mode of action, rivaroxaban 15 mg and rivaroxaban 20 mg 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 (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).

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 rivaroxaban 15 mg and rivaroxaban 20 mg. Therefore, the possibility of a

haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

b. Tabulated summary of adverse reactions

The frequencies of adverse reactions reported with REXARAV are summarised in the table below by system organ class (in MedDRA) and by frequency.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Anaemia (incl. respective laboratory parameters)
	Less frequent	Thrombocytosis (incl. platelet count increased)[A], thrombocytopenia
Immune system disorders	Less frequent	Anaphylactic reactions including anaphylactic shock. Allergic reaction, dermatitis allergic, angioedema and allergic oedema
Nervous system disorders	Frequent	Dizziness, 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, haematoma
Respiratory, thoracic and mediastinal disorders	Frequent	Haemoptysis, epistaxis

MedDRA system organ class	**Frequency**	**Adverse reactions**
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	Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury), abnormal hepatic function, hepatic impairment, increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A]
Skin and subcutaneous tissue disorders	Frequent	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage
	Less frequent	Stevens-Johnson syndrome/ toxic epidermal necrolysis , dress syndrome, urticaria

MedDRA system organ class	**Frequency**	**Adverse reactions**
Musculoskeletal and connective tissue disorders	Frequent	Pain in extremity[A]
	Less frequent	Muscle haemorrhage, haemarthrosis
	Frequency Unknown	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	Localised oedema[A]. Feeling unwell (incl. malaise)
Investigations	Less frequent	Increased LDHA, increased lipase[A], increased amylase[A]
Injury, poisoning and procedural complications	Frequent	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]

MedDRA system organ class	Frequency	Adverse reactions
	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).

* A pre-specified selective approach to adverse event collection was applied. As incidence of adverse reactions did not increase and no new adverse reaction was identified, COMPASS study data were not included for frequency calculation in this table.

c. Description of selected adverse reactions

Due to the pharmacological mode of action, the use of REXARAV 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, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g.

those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (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 REXARAV. 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**”, found online under SAHPRA’s publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

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 REXARAV or above.

A specific antidote antagonising the pharmacodynamic effect of REXARAV not available. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

The use of activated charcoal to reduce absorption in case of REXARAV overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving REXARAV, the next REXARAV 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, either the administration of a specific factor Xa inhibitor reversal medicine (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant reversal medicine, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicines in individuals receiving rivaroxaban. Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of REXARAV. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving REXARAV. There is neither scientific rationale for benefit nor experience with the use of the systemic

haemostatic desmopressin in individuals receiving REXARAV. Due to the high plasma protein binding REXARAV is not expected to be dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacological Classification: A 8.2 Anticoagulants

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 1000 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:

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 (International Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

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) ranged from 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 with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

The oral bioavailability for the 20 mg tablet dose is 66 %, under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39 % were observed when compared to tablet intake under fasting

conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg should be taken with food (see section 4.2).

Under fed conditions rivaroxaban 15 mg and 20 mg 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 a steady-state volume of distribution (Vss) being approximately 50 l.

Biotransformation:

Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 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 the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then eliminated renally and the other half eliminated by the faecal route. The other 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Elimination of rivaroxaban from plasma occurred 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:

Elderly patients:

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 versus > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %) (see section 4,2).

Children and adolescents:

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

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 the five clinical/biochemical measurements composing the Child Pugh classification system, the bleeding risk in patients may not clearly correlate with this classification scheme.

Rivaroxaban is contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

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. No relevant difference in pharmacodynamic properties was observed between these groups.

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. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2,6 as compared to healthy volunteers; prolongation of PT was similarly 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 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).

Renal impairment:

There was an increase in rivaroxaban exposure being inversely correlated to the decrease in renal function, 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) were 1,4; 1,5 and 1,6-fold increased respectively as compared to healthy volunteers (see sections 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced (see sections 4.2 and 4.4).

In individuals with mild, moderate or 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 4.2 and 4.4). Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

Concomitant administration of strong CYP 3A4 inducers:

In a phase I trial, co-administration of rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (see section 4.5).

In a Phase IIb trial, the PK/PD of an adapted rivaroxaban dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP 3A4 and P-gp inducer (rifampicin or phenytoin). The adapted dosing regimen in these patients led to a similar exposure and 190 pharmacodynamics when compared to patients treated for DVT (15 mg twice daily in the first 3 weeks of treatment, followed by 20 mg once daily) without the concomitant administration of a strong CYP 192 3A4 inducer.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Cellulose microcrystalline

Croscarmellose sodium

Hypromellose 2910

Lactose monohydrate

Magnesium stearate

Sodium lauryl sulphate

Film-coat:

Iron oxide red (E 172)

Macrogol (only in 15 mg tablets) / Polyethylene glycol (only in 20 mg tablets)

Polyvinyl alcohol

Talc

Titanium dioxide (E 171)

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

REXARAV film-coated tablets are packed in blister strips (clear, transparent PVC coated with PVdC on one side and hard tempered aluminium foil coated with heat seal lacquer on the other side. Pack sizes: 14 tablets, 28 tablets, 42 tablets, 98

tablets or 100 tablets.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

VIATRIS SOUTH AFRICA (PTY) LTD

4 Brewery Street

Isando

Johannesburg, 1609

Republic of South Africa

8 REGISTRATION NUMBERS

REXARAV 15 mg: 55/8.2/0718

REXARAV 20 mg: 55/8.2/0719

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

July 2023

10 DATE OF REVISION OF THE TEXT