PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

RABOVIX 10 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains rivaroxaban 10 mg.

Contains sugar: lactose monohydrate 20,250 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

A light pink to pink coloured, film-coated, round, biconvex, beveled edge tablet, debossed with RX on one side of the tablet and 2 on the other side.

Dimensions: Diameter 5,4 mm $\pm$ 0,5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

RABOVIX 10 mg film-coated tablets are indicated for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

4.2 Posology and method of administration

Posology

Recommended dose and frequency of administration:

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

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

If a dose is missed the patient should take RABOVIX 10 mg 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

RABOVIX 10 mg 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 RABOVIX 10 mg is administered in patients with mild (creatinine clearance 80 – 50 mL/min) or moderate (creatinine clearance < 50 - 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 RABOVIX 10 mg must be used with caution in these patients (see section 4.4).

Ethnic differences

No dose adjustment is required based on ethnic differences.

Paediatric population (children up to 18 years of age)

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

Method of administration:

Oral use.

RABOVIX 10 mg may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to rivaroxaban or to any of the excipients of RABOVIX (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 RABOVIX must be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. RABOVIX 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 RABOVIX 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 RABOVIX does not require routine monitoring of exposure, ivaroxaban 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. RABOVIX 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).

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

Interaction with other medicines

The use of RABOVIX 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

RABOVIX 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
- recent intracranial or intracerebral haemorrhage
- shortly after brain, spinal or opthalmological surgery.

Patients with prosthetic valves

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

patients.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including RABOVIX 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).

Hip fracture surgery

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

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

RABOVIX 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 RABOVIX 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 10 mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of RABOVIX 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.

For the removal of an epidural catheter at least 18 hours should elapse after the last administration of RABOVIX (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next RABOVIX dose is administered. If traumatic puncture occurs the administration of RABOVIX 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, RABOVIX 10 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. RABOVIX 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. RABOVIX 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

RABOVIX 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 RABOVIX.

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 RABOVIX 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 RABOVIX 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.

No clinically relevant interaction with food was observed (see section 4.2).

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 RABOVIX.

Pregnancy

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

Breastfeeding

Safety and efficacy of RABOVIX have not been established in breastfeeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore RABOVIX is contraindicated during breastfeeding (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

RABOVIX 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 10 mg has been evaluated in three phase III studies including 4571 patients undergoing major orthopaedic surgery of the lower limbs (total hip replacement or total knee replacement) treated up to 39 days. The adverse reactions are presented within each frequency grouping and system organ classes; the adverse reactions should be interpreted within the surgical setting.

b. Tabulated summary of adverse reactions

The frequencies of adverse reactions reported in phase III clinical trials or through post-marketing use with rivaroxaban 10 mg 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	Thrombocytosis (incl. platelet count increased)[A], thrombocytopenia, anaemia (incl.

MedDRA system organ class	Frequency	Adverse reactions
		respective laboratory parameters)
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	Epistaxis, haemoptysis
Gastrointestinal disorders	Frequent	Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]

MedDRA system organ class	Frequency	Adverse reactions
	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), 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
Musculoskeletal and connective tissue disorders	Frequent	Pain in extremity[A]
	Less frequent	Muscle haemorrhage, haemarthrosis
	Frequency Unknown	Compartment syndrome secondary to a bleeding

MedDRA system organ class	Frequency	Adverse reactions
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 LDH[A], increased lipase[A], increased amylase[A]
Injury, poisoning and procedural complications	Frequent	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]
	Less frequent	Vascular pseudoaneurysm[C]
A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. B: observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years.		

MedDRA system organ class	Frequency	Adverse reactions
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 RABOVIX 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 RABOVIX. 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 RABOVIX or above. A specific reversal medicine (andexanet alfa) antagonising the pharmacodynamic effect of Rivaroxaban is available (refer to the professional information of andexanet alfa). The use of activated charcoal to reduce absorption in case of RABOVIX overdose may be considered.

Management of bleeding

Should a bleeding complication arise in a patient receiving RABOVIX, the next RABOVIX 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 RABOVIX. 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 RABOVIX. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving RABOVIX. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving RABOVIX. Due to the high plasma protein binding RABOVIX 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 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 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. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban.

5.2 Pharmacokinetic properties

Absorption:

The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. Rivaroxaban is rapidly 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 %.

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 (V_{ss}) being approximately 50 L.

Biotransformation:

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose) as well as by direct renal excretion of unchanged compound (approximately 1/3). 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.

Elimination

Elimination of rivaroxaban and metabolites occurs via both renal and faecal routes. Approximately 66 % of a rivaroxaban dose is eliminated via the kidneys, with 30 - 40 % excreted as unchanged medicine in the urine via both glomerular filtration and active renal secretion. 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 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/Gender 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).

There were no clinically relevant differences in pharmacokinetics between male and female patients (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:

No data is available for this patient population (see section 4.2).

Inter-ethnic differences

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics (see section 4.2).

Hepatic impairment:

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1,2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. 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. 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 (coagulation Factors VII, X, V, II, I), of which Factors II, VII, and X are synthesised in the liver. The elevated PT at baseline and a significantly altered sensitivity in anticoagulant activity towards rivaroxaban plasma exposure (increase in slope for PT / rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients classified as Child Pugh B indicate the decreased ability of the liver to synthesise coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is

expected to lead to a subsequent increased bleeding risk in this patient group. Therefore rivaroxaban is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 4.3).

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.

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

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:

Macrogol

Polyvinyl alcohol

Iron oxide red (E 172)

Talc

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 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

RABOVIX 10 mg 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. Blister strips contain 5 or 10 tablets per blister.

Pack sizes: 5 tablets, 10 tablets, 30 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 Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng

Republic of South Africa

8 REGISTRATION NUMBERS

RABOVIX 10 mg: 55/8.2/0716.715

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 April 2023

10 DATE OF REVISION OF THE TEXT

04 April 2023