Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

REZALTO 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rivaroxaban.

Each film-coated tablet contains 95,6 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round, biconvex film-coated tablets, engraved with “10” on one side, plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REZALTO 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 recommend dose is one REZALTO once daily for the prevention of various 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 REZALTO 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 populations

Elderly (above 65 years). Gender and body Weight

No dose adjustment is required for these patient populations.

Paediatric population

Children (up to 18 years of age)

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

Patients with impaired liver function

REZALTO is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to 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 REZALTO 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 patient with severe renal impairment (creatinine clearance <30 mL/min) indicated that rivaroxaban plasma levels are significantly increased in this patient population. Therefore REZALTO must be used with caution [~~on~~] in these patients (see section 4.4)

Ethnic differences

No dose adjustment is required based on ethnic differences.

Method of administration

REZALTO is for oral use.

The tablets can be taken with or without food (see sections 4.5 and 5.2).

For patients who are unable to swallow whole tablets, REZALTO may be crushed and mixed with water or apple puree immediately prior to use and administered orally.

The crushed REZALTO tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (see section 5.2).

4.3 Contraindications

- Hypersensitivity to rivaroxaban or to any of the excipients listed in section 6.1.

- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal 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.
- Significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk.
- Pregnancy and lactation (see section 4.6).
- Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (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).
- 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 REZALTO are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. REZALTO administration should be discontinued if severe haemorrhage occurs.

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 Vitamin K Antagonists (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 REZALTO for venous thromboembolism (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 rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (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. REZALTO 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 medicinal products which increase rivaroxaban plasma concentrations REZALTO is to be used with caution (see section 4.5).

Interaction with other medicinal products

The use of REZALTO 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 medicinal products affecting haemostasis such as non-steroidal anti-inflammatory drugs (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,
- recent intracranial or intracerebral haemorrhage,
- shortly after brain, spinal or ophthalmological surgery.

Patients with prosthetic valves

Rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of (Product name) have not been studied in patients with

prosthetic heart valves; therefore, there are no data to support that (Product name) provides adequate anticoagulation in this patient population. Treatment with (Product name) 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 (APS). 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. Treatment of patients with established APS is not recommended (see section 4.3).

Hip fracture surgery

Rivaroxaban 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.

REZALTO 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 REZALTO 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 post-operative use of indwelling epidural catheters or the concomitant use of medicinal

products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the medical practitioner should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

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).

At least 18 hours should elapse after the last administration of rivaroxaban before removal of an epidural catheter. 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 other than elective hip or knee replacement surgery

If an invasive procedure or surgical intervention is required, REZALTO 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.

REZALTO 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. Rivaroxaban 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

REZALTO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose

malabsorption should not take this medicinal product

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of REZALTO 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 Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk.

Therefore, the use of REZALTO 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 Cmax. 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 Cmax. 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 Cmax 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 Cmax 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 Cmax. 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 medicinal products typically increase the bleeding risk (see section 4.4).

SSRIs/SNRIs

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical 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, phenobarbitone 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

Pregnancy

Safety and efficacy of REZALTO have not been established in pregnant women. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, (Product name) is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breastfeeding

Safety and efficacy of REZALTO has not been established in breast-feeding women. REZALTO 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

REZALTO 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

The frequencies of adverse reactions reported with REZALTO are summarised in Table 1 below by system organ class (in MedDRA) and by frequency.

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**
Blood and lymphatic system disorders	Anaemia (incl. Respective laboratory parameters)	Frequent
	Thrombocytosis (incl. platelet count increase)[A], thrombocytopenia	Less frequent
Immune system disorder	Allergic reaction, dermatitis allergic, angioedema, allergic oedema, anaphylactic reactions including anaphylactic shock	Less frequent
Nervous system disorders	Dizziness, headache	Frequent
	Cerebral and intracranial haemorrhage, syncope	Less frequent
Eye disorders	Eye haemorrhage (incl. conjunctival haemorrhage)	Frequent
Cardiac disorders	Tachycardia	Less frequent
Vascular disorders	Hypotension, haematoma	Frequent
Respiratory, thoracic and mediastinal disorders	Epistaxis, haemoptysis	Frequent
Gastrointestinal disorders	Gingival bleeding, gastrointestinal tract	Frequent

	haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation [A], diarrhoea, vomiting [A]	
	Dry mouth	Less frequent
Hepatobiliary disorders	Increase in transaminases	Frequent
	Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase[A], increased GGTA, jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis (incl. hepatocellular injury)	Less frequent
Skin and subcutaneous tissues disorders	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage syndrome	Frequent

	Urticaria, Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis , DRESS	Less frequent
Musculoskeletal and connective tissue disorders	Pain in extremity[A]	Frequent
	Haemarthrosis, muscle haemorrhage	Less frequent
	Compartment syndrome secondary to a bleeding	Unknown
Renal and urinary disorders	Urogenital tract haemorrhage (incl. haematuria and menorrhagia [B]), renal impairment (incl. increased blood creatinine, increased blood urea)	Frequent
	Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion	Unknown
General disorders and administration site conditions	Fever [A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Frequent

	Feeling unwell (incl. malaise), localised oedema [A]	Less frequent
Investigations	Increased LDH[A], increased lipase[A], increased amylase[A]	Less frequent
Injury, poisoning and procedural complications	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion[A]	Frequent
	Vascular pseudoaneurysm[C]	Less frequent
	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 frequent in women < 55 years C: observed as less frequent in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)	

c. Description of selected adverse reactions

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

bleeding and/or anaemia (see section 4.9 “Management of bleeding”). Mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito-urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban 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. 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 (Product name). 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 professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.

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 agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these medicinal 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 limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A.8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, 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 prothrombln 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.

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 - 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 V_{ss} being approximately 50 litres.

Biotransformation and elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion. Approximately 66% of 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.

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. After intravenous administration of a 1 mg dose the elimination half-life is about 4,5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

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. No dose adjustment is necessary.

Different weight categories

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

Inter-ethnic differences

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

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1,2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2,3 fold compared to healthy volunteers. Unbound AUC was increased 2,6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.

The inhibition of factor Xa activity was increased by a factor of 2,6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2,1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

REZALTO 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 - 80 mL/min), moderate

(creatinine clearance 30 - 49 mL/min) and severe (creatinine clearance 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1,4; 1,5 and 1,6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1,5; 1,9 and 2,0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1,3; 2,2 and 2,4 respectively. There are no data in patients with creatinine clearance < 15 mL/min.

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

Use is not recommended in patients with creatinine clearance < 15 ml/min. REZALTO is to be used with caution in patients with creatinine clearance 15 - 29 mL/min (see section 4.4).

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 core:

Cellulose, microcrystalline

Croscarmellose sodium

Hypromellose

Lactose monohydrate

Magnesium stearate

Purified water

Sodium laurilsulfate

Film-coating:

Hypromellose 2910 (E464)

Titanium dioxide (E 171)

Macrogol 3350 (E1521)

Iron oxide red (E 172)

6.2 Incompatibilities

Not applicable**.**

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 ^{o}C.

6.5 Nature and contents of container

Tablets are packed in transparent PVC/Aluminium blister strips of 7 or 10, which are further packed in printed cartons, in pack sizes of 10 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER(S)

REZALTO 10 mg: 53/8.2/0194

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 November 2020

10. DATE OF REVISION OF THE TEXT