1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. Name of the medicinal product

AZIRIV 10 mg film-coated tablets

AZIRIV 15 mg film-coated tablets

AZIRIV 20 mg film-coated tablets

2. Qualitative and quantitative composition

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

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

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

Excipient with known effect

Each 10 mg film-coated tablet contains 27,90mg lactose (as monohydrate), see section 4.4.

Each 15 mg film-coated tablet contains 25,40mg lactose (as monohydrate), see section 4.4.

Each 20 mg film-coated tablet contains 22,90mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

10 mg film-coated tablet: Blue, biconvex, round, film coated tablets debossed “10” on one side, plain on other side.

15 mg film-coated tablet: White, biconvex, round, film coated tablets debossed “15” on one side, plain on other side.

20 mg film-coated tablet: Deep red, biconvex, round, film coated tablets debossed “20” on one side, plain on other side.

4. Clinical particulars

4.1 Therapeutic indications

AZIRIV 10 is indicated for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

AZIRIV 15 & 20 are indicated for:

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

4.2 Posology and method of administration

Posology

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

VTE – Recommended usual dose and frequency of administration:

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

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

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

VTE – 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.

VTE – Special patient populations

VTE – Elderly (above 65 years), Gender and Body Weight:

No dose adjustment is required for these patient populations.

VTE – Children (up to 18 years of age)

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

VTE – Patients with impaired liver function

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

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

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

VTE – Patients with impaired renal function

No dose adjustment is required if AZIRIV 10 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 AZIRIV 10 must be used with caution in these patients (see section 4.4).

VTE – Ethnic differences

No dose adjustment is required based on ethnic differences.

SPAF – Recommended usual dose and frequency of administration:

The recommended dose is one AZIRIV 20 tablet once daily.

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

AZIRIV tablets should be taken with food.

SPAF – Duration of treatment:

Therapy should be continued as long as risk factors for stroke and systemic embolism persist.

SPAF – Missed dose:

If a dose is missed the patient should take AZIRIV 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 AZIRIV 20 tablet (20 mg rivaroxaban).

SPAF – Additional information on special populations:

SPAF – Patients with hepatic impairment:

AZIRIV 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 section 4.3 & section 5.2).

SPAF – Patients with renal impairment:

No dose adjustment is required if AZIRIV 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 ml/min) renal impairment. For patients with moderate (creatinine clearance < 50 to 30 ml/min) renal impairment the recommended dose is one AZIRIV 15 once daily.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore AZIRIV 15 must be used with caution in these patients.

Use of AZIRIV is not recommended in patients with creatinine clearance < 15 ml/min (see section 4.4 & section 5.2).

SPAF – Converting from warfarin to AZIRIV*:*

Warfarin treatment should be stopped and AZIRIV therapy should be initiated when the INR is ≤ 3,0. When converting patients from warfarin to AZIRIV, INR values will be falsely elevated after the intake of AZIRIV. The INR is not valid to measure the anticoagulant activity of AZIRIV, and therefore should not be used (see section 4.5).

SPAF – Converting from AZIRIV *to warfarin:*

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

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

AZIRIV). Once AZIRIV is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF – Converting from parenteral anticoagulants to AZIRIV*:*

For patients currently receiving a parenteral anticoagulant, start AZIRIV, 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 AZIRIV *to parenteral anticoagulants:*

Discontinue AZIRIV and give the first dose of parenteral anticoagulant at the time that the next AZIRIV 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 AZIRIV 15 tablet twice daily for the first three weeks followed by one AZIRIV 20 tablet once daily for the continued treatment and the prevention of recurrent DVT and PE.

AZIRIV tablets should be taken with food.

DVT and PE treatment – Duration of treatment:

Therapy should be continued as long as the VTE risk persists.

DVT and PE treatment – Missed dose:

It is essential to adhere to the dosage schedule provided.

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

If a dose is missed during the AZIRIV 20 once daily treatment phase the patient should take AZIRIV 20 immediately to ensure intake of 20 mg per day. The patient should continue with the regular one AZIRIV 20 once daily intake as recommended on the following day.

DVT and PE treatment – Maximum daily dose:

The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment.

In the following treatment phase the recommended maximum daily dose is 20 mg.

DVT and PE treatment – Additional information on special populations:

DVT and PE treatment – Patients with hepatic impairment:

AZIRIV is 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 section 4.3 and section 5.2).

DVT and PE treatment – Patients with renal impairment:

No dose adjustment is required if AZIRIV 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, AZIRIV must be used with caution in these patients.

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

DVT and PE treatment – Converting from warfarin to AZIRIV 15*:*

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

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

DVT and PE treatment – Converting from AZIRIV *to warfarin:*

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

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

For patients currently receiving a parenteral anticoagulant, start AZIRIV 15, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

DVT and PE treatment – Converting from AZIRIV *to parenteral anticoagulants:*

Discontinue AZIRIV and give the first dose of parenteral anticoagulant at the time that the next AZIRIV dose would have been taken.

DVT and PE treatment – Children and adolescents (from birth to 18 years):

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

DVT and PE treatment – Body weight:

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

Method of administration:

Oral use.

AZIRIV tablets should be taken with food.

4.3 Contraindications

AZIRIV are contra-indicated in patients with:

- Hypersensitivity to rivaroxaban or any excipient listed in section 6.1.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- Hepatic disease with or without coagulopathy.
- Patients with persistent triple positive antiphospholipid syndrome (APS)
- Pregnancy and breastfeeding (see section 4.6).

4.4 Special warnings and precautions for use

Patients with prosthetic valves:

Safety and efficacy of AZIRIV have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that AZIRIV 20 (AZIRIV 15 in patients with moderate or severe renal impairment) provides adequate anti-coagulation in this patient population.

Patients with antiphospholipid syndrome (APS)

Treatment of patients with established APS is not recommended as evidence regarding safety and efficacy, including the benefit/harm balance of rivaroxaban (and direct acting oral anticoagulants (DOACs) with the same mechanism of action) in APS patients, is inconclusive. There is some evidence that treatment of persistently triple positive APS patients with rivaroxaban is associated with an increased risk of recurrent arterial thrombotic events compared with treatment of these patients with warfarin; a vitamin K antagonist (see section 4.3).

Bleeding risk:

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

- Congenital or acquired bleeding disorders
- Uncontrolled severe arterial hypertension
- Active ulcerative gastrointestinal disease
- Recent gastrointestinal ulcerations

- Vascular retinopathy
- Recent intracranial or intracerebral haemorrhage
- Intraspinal or intracerebral vascular abnormalities
- Shortly after brain, spinal or ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding.

Care should be taken if patients are treated concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory medicines (NSAIDs), platelet aggregation inhibitors, or other antithrombotics (see section 4.5).

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

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

Surgery and interventions:

If an invasive procedure or surgical intervention is required, AZIRIV should be stopped at least 24 hours before the intervention, if possible and based on clinical judgement of the medical practitioner.

If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

AZIRIV should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 5.2).

Neuraxial (epidural/spinal) anaesthesia:

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

The risk of these events is further increased by 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 punctures.

Patients should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The medical practitioner should consider the potential benefit versus the risk before neuraxial intervention in patients who are anticoagulated or considered to be anticoagulated for thromboprophylaxis.

An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of AZIRIV.

AZIRIV should be administered not before 6 hours after the removal of the catheter.

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

DVT and PE treatment – Renal impairment:

AZIRIV is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (see section 4.5).

SPAF, DVT and PE treatment – Renal impairment:

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly elevated (1,6-fold on average) which may lead to an increased bleeding risk. Due to the underlying disease these patients are at an increased risk of both bleeding and thrombosis.

Due to limited clinical data AZIRIV should be used with caution in patients with creatinine clearance < 30 to 15 ml/min.

No clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min). Therefore, the use of AZIRIV is not recommended in these patients (see section 4.2; section 5.1 & 5.2).

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

Concomitant medication:

AZIRIV is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These medicines are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these medicines may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see section 4.5).

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

QTc prolongation:

No QTc prolonging effect was observed with AZIRIV.

Lactose

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take AZIRIV.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban 10 mg (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 (see section 4.4).

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 times was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels (see section 4.4).

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 more pronounced pharmacodynamic response (see section 4.4).

Converting patients from 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 15 mg or 20 mg during the conversion period, anti-Factor Xa activity, prothrombinase-induced clotting time (PiCT), and HepTest® can be used as these tests were not affected by warfarin.

From day 4 after stopping warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban 15 mg or 20 mg (see section 4.2).

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.

Pharmacokinetic interactions:

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp)/breast cancer resistance protein (Bcrp) transporter systems (see section 5.2).

CYP inhibition:

Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.

CYP induction:

Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

Effects on AZIRIV*:*

The concomitant use of rivaroxaban 10 mg or 20 mg with strong CYP 3A4 and P-gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure. Co-administration of rivaroxaban with the azole-antimycotic ketoconazole (400 mg once daily) a strong CYP 3A4 and P-gp inhibitor, led to a 2,6-fold increase in mean rivaroxaban steady state AUC and a 1,7-fold increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects (see section 4.4).

Co-administration of rivaroxaban with the HIV protease inhibitor ritonavir (600 mg twice daily), a strong CYP 3A4 and P-gp inhibitor, led to a 2,5-fold increase in mean rivaroxaban AUC and a 1,6-fold

increase in mean rivaroxaban C_{max}, with significant increases in its pharmacodynamic effects. Data on the co-administration of rivaroxaban with the HIV protease inhibitor ritonavir (100 mg twice daily) is not available.

Therefore, AZIRIV are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see section 4.4).

Other active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent.

Clarithromycin (500 mg twice daily), considered a strong CYP 3A4 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}. This increase, which is close to the magnitude of the normal variability of AUC and C_{max}, is considered as clinically not relevant.

Erythromycin (500 mg three times daily), which inhibits CYP 3A4 and P-gp moderately, led to a 1,3-fold increase in mean rivaroxaban AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered as clinically not relevant.

Fluconazole (400 mg once daily), considered a moderate CYP 3A4 inhibitor, led to a 1,4-fold increase in mean rivaroxaban AUC and a 1,3-fold increase in mean C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered as clinically not relevant.

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 5.2).

The concomitant use of rivaroxaban 15 mg or 20 mg with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to a decreased rivaroxaban plasma concentration. Strong CYP 3A4 inducers should be co-administered with caution.

Interactions shown not to exist:

There were no mutual pharmacokinetic interactions between rivaroxaban and midazolam (substrate of CYP 3A4), digoxin (substrate of P-glycoprotein) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the proton pump inhibitor omeprazole, the H2 receptor antagonist ranitidine, the antacid aluminium hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Interactions with laboratory parameters:

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of rivaroxaban.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

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

Pregnancy:

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

Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, AZIRIV is contra-indicated in pregnancy (see section 4.3).

Breastfeeding:

Safety and efficacy of AZIRIV have not been established in nursing mothers. In rats rivaroxaban is secreted into breast milk. Therefore, AZIRIV may only be administered after breastfeeding is discontinued (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

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

4.8 Undesirable effects

Due to the pharmacological mode of action, AZIRIV 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. Therefore, the possibility of a haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

Adverse reactions classified by system organ class and MedDRA are presented in the table below (Table 1).

Table 1: Tabulated list of adverse reactions (MedDRA) from reported placebo-controlled studies and from post-marketing experience

System organ class	Frequent	Less frequent	Frequency unknown
Blood and the lymphatic system disorders	Anaemia (incl. respective laboratory parameters)	Thrombocythaemia (incl. platelet count increased)	
Cardiac disorders		Tachycardia	

Eye disorders	Eye haemorrhage (incl. conjunctival haemorrhage)		
Gastrointestinal disorders	Gingival bleeding Gastrointestinal tract haemorrhage (incl. rectal haemorrhage) Gastrointestinal and abdominal pains Dyspepsia (incl. epigastric discomfort) Nausea Constipation [A] Diarrhoea Vomiting [A]	Dry mouth	
General disorders and administration site conditions	Fever [A] Peripheral oedema Decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise) Localised oedema [A]	
Hepato-biliary disorders		Abnormal hepatic function Jaundice Cholestasis, Hepatitis (incl. hepatocellular injury)	
Immune system disorders		Allergic reaction Allergic dermatitis Angioedema and	

		allergic oedema, Anaphylactic reactions including anaphylactic shock	
Injury, poisoning and post-procedural complications	Post-procedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage) Contusion Wound secretion [A]	Vascular pseudoaneurysm [C]	
Investigations	Increase in transaminases	Increase in bilirubin Increase in blood alkaline phosphatase [A] Increase in LDH [A] Increase in lipase [A] Increase in amylase [A] Increase in GGT [A] Increase in conjugated bilirubin (with or without concomitant increase of ALT)	
Musculoskeletal, connective tissue and bone disorders	Pain in extremity [A]	Haemarthrosis Muscle haemorrhage	Compartment syndrome secondary to a bleeding and connective tissue disorders)
Nervous system	Dizziness	Cerebral and intracranial	

disorders	Headache	haemorrhage Syncope	
Renal and urinary disorders	Urogenital tract haemorrhage (incl. haematuria and menorrhagia [B]) Renal impairment (incl. blood creatinine increased, blood urea increased) [A]		Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
Respiratory tract thoracic and mediastinal disorders	Epistaxis Haemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalised pruritus) Rash Ecchymosis Cutaneous and subcutaneous haemorrhage	Urticaria, Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis, DRESS syndrome	
Vascular disorders	Hypotension Haematoma		

[A] observed after major orthopaedic surgery of the lower limbs

[B] observed in VTE treatment as very frequent in women < 55 years

[C] observed as less frequent in prevention therapy in ACS (following percutaneous intervention)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions.

Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above.

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, either the administration of a specific factor Xa inhibitor reversal agent (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 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

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 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:

Dose dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0,98) if Neoplastin® is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (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 4.1).
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 V_{ss} being approximately 50 L.

Biotransformation and 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.

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 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).

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 drug 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 section 4.1 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 section 4.1 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced (see section 4.1 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 section 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 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 3A4 inducer.

Paediatric populations:

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

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose sodium

Hypromellose

Sodium lauryl sulphate

Magnesium stearate

Film coating

Hypromellose

Titanium dioxide

Talc (20 mg)

Macrogol

Iron oxide red (20 mg) or FD&C Blue #2 (10 mg)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

Store in the original package until use

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

PVC/PVdC-peel push blister pack

Pack sizes of 10, 28, 30, 56, 60, 90 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

AZIRIV 10: 55/8.2/0492.489

AZIRIV 15: 55/8.2/0493.490

AZIRIV 20: 55/8.2/0494.491

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT