Professional Information

SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

EMBIRIV 10 (FILM COATED TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Contains sugar (lactose monohydrate – 21,0 mg per 10 mg tablet)

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM

Film coated tablets

EMBIRIV 10 round pink, biconvex film coated tablets, debossed with “L” on one side and “10” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EMBIRIV 10 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 **EMBIRIV 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 **EMBIRIV 10** immediately and continue on the following day with the once daily intake as before.

Duration of treatment

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

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

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

Special populations

Elderly Population

No dose adjustment is required for these patient populations.

Hepatic Impairment

EMBIRIV 10 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 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.

Renal Impairment

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

Paediatric Population

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

Method of administration

For oral use

EMBIRIV 10 may be taken with or without food.

4.3 Contraindications

EMBIRIV 10 is contraindicated in patients with:

- Hypersensitivity to the rivaroxaban or to any of the excipients listed in section 6.1
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk.
- Pregnancy and lactation (see section 4.6).
- 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)

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 **EMBIRIV 10** are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. **EMBIRIV 10** 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 **EMBIRIV 10** treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8).

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

Although treatment with **EMBIRIV 10** does not require routine monitoring of exposure, **EMBIRIV 10** levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of **EMBIRIV 10** exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

Renal impairment

EMBIRIV 10 should be used with caution in patients with renal impairment concomitantly receiving other medicines which increase **EMBIRIV 10** plasma concentrations (see section 4.5).

In patients with severe renal impairment (creatinine clearance < 30 mL/min) **EMBIRIV 10** plasma levels may be significantly increased which may lead to an increased bleeding risk and thrombosis.

EMBIRIV 10 is to be used with caution in patients with creatinine clearance < 30 to 15 mL/min. Use is not recommended in patients with creatinine clearance < 15 mL/min (see sections 4.2 and 5.2).

Interaction with other medicines

The use of **EMBIRIV 10** 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 **EMBIRIV 10** plasma concentrations to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk (see section 4.5).

Care is to be taken if patients are treated concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory medicines (NSAIDs), acetylsalicylic acid 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).

Bleeding risk factors:

EMBIRIV 10 should be used with caution in patients with an increased bleeding risk such as:

- Congenital or acquired bleeding disorders
- Uncontrolled severe arterial hypertension

- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- Vascular retinopathy
- Recent intracranial or intracerebral vascular abnormalities
- Shortly after brain, spinal ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding

Patients with prosthetic valves

EMBIRIV 10 should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Treatment with **EMBIRIV 10** is not recommended for these patients.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including **EMBIRIV 10** 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.

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.

EMBIRIV 10 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 **EMBIRIV 10** 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 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.

To reduce the potential risk of bleeding associated with the concurrent use of **EMBIRIV 10** and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of **EMBIRIV 10**. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of **EMBIRIV 10** is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is unknown.

For the removal of an epidural catheter and based on the general PK characteristics at least 2 x half-life, i.e. at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of **EMBIRIV 10** (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next **EMBIRIV 10** dose is administered.

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

Invasive procedures and surgical interventions:

If an invasive procedure or surgical intervention is required, **EMBIRIV 10** should be stopped at least 24 hours before the intervention, if possible and based on clinical judgment of the medical practitioner.

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

EMBIRIV 10 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”).

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. **EMBIRIV 10** 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.

QTc prolongation

No QTc prolonging effect was observed with **EMBIRIV 10.**

Women of childbearing potential

EMBIRIV 10 should be used in woman of childbearing potential only with effective contraception (see section 4.6).

Information about excipients:

EMBIRIV 10 contain lactose, Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **EMBIRIV 10.**

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** elimination pathways, either CYP3A4 or P-gp, are expected to increase **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** 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 **EMBIRIV 10** should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with **EMBIRIV 10** (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 **EMBIRIV 10**.

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 **EMBIRIV 10** 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 **EMBIRIV 10** 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 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 **EMBIRIV 10** (20 mg) or from **EMBIRIV 10** (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 **EMBIRIV 10** 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 **EMBIRIV 10**

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 **EMBIRIV 10** (24 hours after the previous intake of **EMBIRIV 10**) as this test is minimally affected by **EMBIRIV 10** at this time point.

No pharmacokinetic interaction was observed between warfarin and **EMBIRIV 10**.

CYP3A4 inducers

Co-administration of **EMBIRIV 10** with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean **EMBIRIV 10** AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of **EMBIRIV 10** with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort *(Hypericum perforatum)*) may also lead to reduced **EMBIRIV 10** 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 **EMBIRIV 10** 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). **EMBIRIV 10** neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of **EMBIRIV 10** (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

EMBIRIV 10 should be used in woman of childbearing potential only with effective contraception.

Pregnancy

Safety and efficacy of **EMBIRIV 10** have not been established in pregnant woman. In rats and rabbits **EMBIRIV 10** showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g. haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that **EMBIRIV 10** passes the placenta, **EMBIRIV 10 is** contraindicated in pregnancy (see “section 4.3”)

Breast-feeding

Safety and efficacy of **EMBIRIV 10** have not been established in nursing mothers. In rats **EMBIRIV 10** is secreted into breast milk. Therefore **EMBIRIV 10** 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. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Syncope and dizziness have been reported and may affect the ability to drive and use machines (see “section 4.8”). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effect

Blood and the lymphatic system disorders:

Frequent: Anaemia (including respective laboratory parameters)

Less frequent: Thrombocythemia (incl. platelet counts increased), thrombocytopaenia

Immune system disorders:

Less frequent: Allergic reaction, allergic dermatitis, angioedema and allergic oedema, anaphylactic reactions including anaphylactic shock.

Nervous system disorder:

*Frequent***:** Dizziness, headache

Less frequent: Cerebral and intracranial haemorrhage, syncope

Eye disorders:

*Frequent***:** Eye haemorrhage (Incl. conjunctival haemorrhage)

Cardiac disorders:

Less frequent: Tachycardia

Vascular disorder:

*Frequent***:** Hypotension, haematoma

Respiratory tract disorder:

*Frequent***:** Epistaxis, haemoptysis

Gastrointestinal disorders:

*Frequent***:** Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation, diarrhoea, vomiting

Less frequent: Dry mouth

Hepato-biliary disorders:

Frequent: Increase in transaminases

Less frequent: Abnormal hepatic function, jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), cholestasis, hepatitis, (including hepatocellular injury).

Skin and subcutaneous tissue disorder:

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

Less frequent: Urticaria, Stevens- Johnson syndrome/toxic epidermal necrolysis, DRESS syndrome

Musculoskeletal, connective tissue and bone disorders:

*Frequent***:** Pain in extremity

Less frequent: Haemarthrosis, muscle haemorrhage

Frequency unknown: compartment syndrome secondary to a bleeding

Renal and urinary disorder:

*Frequent***:** Urogenital tract haemorrhage (incl. haematuria and menorrhagia), 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, peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia

Less frequent: Feeling unwell (incl. malaise), localised oedema

Investigations:

Less frequent: Increased LDH, increased lipase, increased amylase

Injury, poisoning and postprocedural complications:

*Frequent***:** Postprocedural haemorrhage (incl. postoperative anaemia and wound haemorrhage), contusion, wound secretion

Less frequent: Vascular pseudoaneurysm

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 Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdose following administration of **EMBIRIV 10** may lead to haemorrhagic complications due to its pharmacodynamic properties.

The use of activated charcoal to reduce absorption in case of **EMBIRIV 10** overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban.

Due to the high plasma protein binding **EMBIRIV 10** is not expected to be dialysable. Should bleeding occur, management of the haemorrhage may include the following steps:

- Delay of next **EMBIRIV 10** administration or discontinuation of treatment as appropriate.

Rivaroxaban has a half-life of approximately 5 to 13 hours.

- Appropriate symptomatic treatment, e.g. mechanical compression (e.g., for severe epistaxis), surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- Activated prothrombin complex concentrate (APCC)
- Prothrombin complex concentrate (PCC)
- Recombinant Factor VIIa (rF VIIa).

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of **EMBIRIV 10**. There is no scientific rationale for benefit or experience with systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving **EMBIRIV 10**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1 000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increase 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 by humans.

Pharmacodynamic effects:

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15 s).

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

5.2 Pharmacokinetic properties

Absorption and bioavailability:

The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (Cmax) 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).

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

Distribution:

Plasma protein binding in humans is high approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with Vss being approximately 50 L.

Biotransformation and elimination:

Biotransformation

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 CYP3A4, CYP 2J2 and CYP-independent mechanism. 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).

Elimination

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.

Linearity/non-linearity

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

Special populations:

Elderly:

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:

Extreme 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:

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 patients, 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 patients; 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 section 4.2 and 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 patients; 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. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 mL/min (see section 4.4)

Pharmacokinetic data in patients

In patients receiving rivaroxaban for prevention of VTE 10 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7 - 273) and 14 (4 - 51) mcg/L, respectively.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been

evaluated after administration of a wide range of doses (5 - 30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an Emax model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/ (100 mcg/L). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects. In patients, baseline factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

Paediatric Population:

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

5.3 Pre-Clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light-coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

EMBIRIV 10 – Lactose monohydrate, croscarmellose sodium, hypromellose, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate, opadry pink, titanium dioxide, macrogol / peg, iron oxide red.

6.2 Incompatibilities

None

6.3 Shelf life

36 months from manufacturing

6.4 Special Precautions for storage

Store at or below 30 °C in original container, protect from moisture and light.

Do not remove blister card from the carton until required for use.

6.5 Nature and contents of container

EMBIRIV 10 (rivaroxaban) film-coated tablets are available as follows: A carton containing aluminium foil and transparent PVC/PVDC blister strips containing 10 tablets each and 3 blister strips per pack.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be returned to the pharmacy for destruction or it must be disposed of in accordance with local requirements for medical waste destruction.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd.

14 Lautre Road, Stormill, Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBERS

EMBIRIV 10: 55/8.2/0317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2022

10. DATE OF REVISION OF THE TEXT

27 November 2024