Professional Information

SCHEDULING STATUS

S4

1. NAME OF MEDICINE:

EMBIRIV 15 (FILM COATED TABLETS)

EMBIRIV 20 (FILM COATED TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Contains sugar (lactose monohydrate – 31,5 mg per 15 mg tablet)

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

Contains sugar (lactose monohydrate – 42,0 mg per 20 mg tablet)

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

3. PHARMACEUTICAL FORM

Film coated tablets

EMBIRIV 15 round brown, biconvex film coated tablets, debossed with “504” on one side and plain on the other side.

EMBIRIV 20 triangle shaped, brown, film coated tablets, debossed with “505” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

EMBIRIV is indicated for:

Sign:

- 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

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

SPAF – **Recommended usual dose and frequency administration:**

The recommended dose is one **EMBIRIV 20** mg tablet once daily. For patients with moderate renal impairment (creatinine clearance < 50 to 30 mL/min) the recommended dose is one **EMBIRIV 15 mg tablet** daily.

EMBIRIV should be taken with food.

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

If a dose is missed the patient should take **EMBIRIV 15** or **EMBIRIV 20** 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 daily dose is one **EMBIRIV 20**

SPAF – Additional information on special populations:

SPAF – Patients with hepatic impairment.

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

SPAF – Patients with renal impairment:

Sign:

No dose adjustment is required if **EMBIRIV 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 15 mg once daily.

EMBIRIV plasma levels are significantly increased in patients with severe renal impairment. Therefore **EMBIRIV 15** must be used with caution in these patients.

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

*SPAF – Converting from warfarin to **EMBIRIV:***

Warfarin treatment should be stopped and **EMBIRIV** therapy should be initiated when the INR is ≤ 3,0.

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

*SPAF – Converting from **EMBIRIV** to warfarin:*

There is a potential for inadequate anticoagulation during the translation from **EMBIRIV** to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that **EMBIRIV** can contribute to an elevated INR. In patients converting from **EMBIRIV** to warfarin, warfarin should be given concurrently until the INR is ≥ 2,0. For the first two days of the conversation period, standard warfarin dosing should be used followed by warfarin dosing guided by INR testing. While patients are on both **EMBIRIV** and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of **EMBIRIV).** Once **EMBIRIV** is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF – *Converting from parenteral anticoagulants to **EMBIRIV:***

Sign:

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

Discontinue **EMBIRIV** and give the first dose of parenteral anticoagulants at the time that the next **EMBIRIV** dose would have been taken.

SPAF – Children and adolescent (from birth to 18 years):

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

SPAF – Body weight:

No dose adjustment is required based on body weight (see “Pharmacokinetic properties”).

DVT and PE treatment – Recommended usual dose and frequency of administration:

The recommended dose for the initial treatment of acute DVT and PE is 15 mg **twice daily** for the first three weeks followed by one **20 mg** tablet **once daily** for the continued treatment and the prevention of recurrent DVT and PE.

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

Sign:

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

***DVT and PE treatment** – Maximum daily dose:*

The maximum daily dose is 30 mg during the first three weeks of treatment. In the following treatment phase the recommended maximum daily dose is 20 mg.

DVT and PE treatment – Patients with hepatic impairment:

EMBIRIV 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 5.2)

***DVT and PE treatment – Patients with renal impairment*:**

No dose adjustment is required if **EMBIRIV** 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 “Pharmacokinetic properties”).

EMBIRIV plasma levels are significantly increased in patients with severe renal impairment (creatinine clearance < 30 to 15 mL/min). **EMBIRIV** must therefore be used with caution in these patients.

Use of **EMBIRIV** 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 EMBIRIV 15:

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

Sign:

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

DVT and PE treatment – Converting from EMBIRIV to warfarin:

There is a potential for inadequate anticoagulation during the transition from **EMBIRIV** to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that **EMBIRIV** can contribute to an elevated INR. In patients converting from **EMBIRIV** 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 **EMBIRIV** and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of **EMBIRIV.** Once **EMBIRIV** is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

DVT and PE treatment – Converting from parental anticoagulants to EMBIRIV 15:

For patients currently receiving a parental anticoagulant, start **EMBIRIV 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 parental medicine (e.g. intravenous unfractionated heparin).

DVT and PE treatment – Converting from EMBIRIV to parenteral anticoagulants:

Discontinue **EMBIRIV** and give the first dose of parenteral anticoagulant at the time that the next **EMBIRIV** 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 “Pharmacokinetic properties”).

Sign:

4.3 Contraindications

EMBIRIV is contraindicated in patients with:

- Hypersensitivity to rivaroxaban or any excipient of the tablets.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- Hepatic disease with or without coagulopathy.
- **EMBIRIV** is contraindicated throughout pregnancy (see “section 4.6”).
- **EMBIRIV** is contraindicated during breastfeeding and may only be administered after breastfeeding is discontinued (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).

4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period**.**

Sign:

Haemorrhagic risk

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

Patients with prosthetic valves

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

Sign:

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including **EMBIRIV** 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.
Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy

EMBIRIV 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** have not been established in these clinical situations.

Other bleeding risk factors:

EMBIRIV 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 ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding

Sign:

Interaction with other medicines

The use of **EMBIRIV** 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** 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).

Renal impairment

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

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

EMBIRIV 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).

Sign:

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

Invasive procedures and surgical interventions:

If an invasive procedure or surgical intervention is required, **EMBIRIV** 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 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”).

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.

There is no clinical experience with the use of 15 mg or 20 mg **EMBIRIV** in these situations.

Sign: 

To reduce the potential risk of bleeding associated with the concurrent use of **EMBIRIV** and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of **EMBIRIV**. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of **EMBIRIV** 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** (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next **EMBIRIV** dose is administered.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Women of childbearing potential

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

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** 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.

Sign: 

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

Clinical data are available from an interventional study with the primary objective to assess safety in patients with nonvalvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/TIA.

QTc prolongation

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

Information about excipients:

Since **EMBIRIV** contain lactose, patients with rare hereditary problems of lactose or galactose intolerance (e.g. the Lapp lactose deficiency or glucose-galactose malabsorption) should not take **EMBIRIV.**

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of **EMBIRIV** 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** 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** elimination pathways, either CYP3A4 or P-gp, are expected to increase **EMBIRIV** plasma concentrations to a lesser extent.

Sign:

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** 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** 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** 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** 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** 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** should be avoided.

Anticoagulants

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

Sign:

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** (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 **EMBIRIV** 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 **EMBIRIV** (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicines typically increase the bleeding risk (see section 4.4).

SSRIs/SNRIs

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

Sign:

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** 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**

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

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

CYP3A4 inducers

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

Laboratory parameters

Sign:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

Safety and efficacy of **EMBIRIV** have not been established in pregnant woman. In rats and rabbits **EMBIRIV** showed pronounced material 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** passes the placenta, **EMBIRIV** is contraindicated in pregnancy (see “section 4.3”)

Breast-feeding

Safety and efficacy of **EMBIRIV** have not been established in nursing mothers. In rats **EMBIRIV** is secreted into breast milk. Therefore **EMBIRIV** may only be administered after breastfeeding is discontinued (see “section 4.3”).

Fertility

Sign:

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:

Sign:

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, Steven 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

Sign:

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 Drug Reactions 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 celling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above. A specific antidote antagonising pharmacodynamics effect of **EMBIRIV** is not available. The use of activated charcoal to reduce absorption in case of **EMBIRIV** overdose may be considered. Due to the high plasma protein binding **EMBIRIV** is not expected to be dialysable. Managing of bleeding:

Sign:

Should a bleeding complication arise in a patient receiving **EMBIRIV**, the next administration should be delayed or treatment should be discontinued as appropriate. **EMBIRIV** has a half-life of approximately 5 to 13 hours. 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 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 products in individuals receiving **EMBIRIV**.

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of **EMBIRIV**.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving **EMBIRIV**. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving **EMBIRIV**.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action:

Sign:

EMBIRIV 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:

Does dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by **EMBIRIV** 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 **EMBIRIV** 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 **EMBIRIV** for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin®) 1 to 4 hours after tablet

Sign:

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 pharmacodynamics effect of rivaroxaban**.**

Anti-factor Xa activity is also influenced by rivaroxaban, however no standard for calibration is available.

5.2 Pharmacokinetic properties

Absorption and bioavailability:

EMBIRIV is rapidly absorbed with maximum concentration (C_{max}) appearing 2 to 4 hours after tablet intake. The oral bioavailability for the 20 mg tablet dose is 66 %, under fasting condition. When **EMBIRIV** 20 mg tablets are taken together with food increase in mean AUC by 39 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. **EMBIRIV** 15 mg and 20 mg should be taken with food (see “section 4.2”)

Under fed conditions **EMBIRIV** 15 mg and 20 mg tablets demonstrated dose-proportionality.

Variability in **EMBIRIV** 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.

Metabolism and elimination:

Sign:

Of the administered **EMBIRIV** 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.

EMBIRIV is metabolised via CYP 2J2 and CYP-independent mechanism. Oxidative degradation of the morpholinone moiety and hydrolysis of the amid bonds are the major sites of biotransformation. Based on *in vitro* investigations **EMBIRIV** is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged **EMBIRIV** 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 **EMBIRIV** can be classified as a low-clearance substance. Elimination of **EMBIRIV** 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:

Geriatric 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:

Extreme in body weight (< 50 kg versus > 120 kg) had only a small influence on **EMBIRIV** plasma concentrations (less than 25 %) (see section 4.2).

Children and adolescents:

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

Sign:

Hepatic impairment:

The effect of hepatic impairment on rivaroxaban pharmacokinetics has been studied in subjects categorised according 10 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 m 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

Sign:

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 4.2 and 4.3).

Renal impairment:

There was an increase in **EMBIRIV** exposure being inversely correlated to the decrease in renal function, as assessed via creatinine clearance measurement.

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, **EMBIRIV** plasma concentrations (AUC) were 1,4; 1,5 and 1,6-fold increased respectively as compared to healthy volunteers (see section 4.4 and section 4.2).

Corresponding increase in pharmacodynamics effects were more pronounced (see “section 4.4” and “section 4.2”).

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.

EMBIRIV is to be used with caution in patients with severe renal impairment (creatinine clearance < 30 to 15 mL/min) (see section 4.2 and section 4.4). Due to the underlying disease patients with severe renal impairment are at increased risk of both bleeding and thrombosis.

Concomitant administration of strong CYP 3A4 inducers:

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

Sign:

In a Phase IIb trail, the PK/PD of an adapted **EMBIRIV** dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 17 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.

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

Sign:

Excipients:

EMBIRIV 15 – Lactose monohydrate, croscarmellose sodium, hypromellose, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate, opadry brown, titanium dioxide, macrogol / peg, iron oxide red, ferrosoferric oxide (NF) black.

EMBIRIV 20 – Lactose monohydrate, croscarmellose sodium, hypromellose, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate, opadry brown, titanium dioxide, macrogol / peg, iron oxide red, ferrosoferric oxide (NF) black.

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 (rivaroxaban) film-coated tablets are available as follows: A carton containing aluminium foil and transparent PVC/PVDC blister strips containing 10 or 14 tablets each.

The packs contain:

pack size of 15 mg is 3 x 14 tablets

pack size of 20 mg is 2 x 14 tablets

6.6 Special precautions for disposal and other handling

Sign:

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 15 mg: 55/8.2/0318

EMBIRIV 20 mg: 55/8.2/0319

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2022

10. DATE OF REVISION OF THE TEXT

TBI

Sign: