

SCHEDULING STATUS

S4

PROPRIETARY NAME (and dosage form)**RIVAXORED 10** (Film-coated tablets)**RIVAXORED 15** (Film-coated tablets)**RIVAXORED 20** (Film-coated tablets)**COMPOSITION****RIVAXORED 10:** Each film-coated tablet contains rivaroxaban 10 mg.**RIVAXORED 15:** Each film-coated tablet contains rivaroxaban 15 mg.**RIVAXORED 20:** Each film-coated tablet contains rivaroxaban 20 mg.**Other ingredients:**

Tablet core: cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cps, lactose monohydrate, magnesium stearate, sodium lauryl sulfate.

Film-coat: iron oxide red E172, hypromellose, macrogol, talc (**RIVAXORED 20**), titanium dioxide E171.

Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION

A 8.2 Anticoagulants

PHARMACOLOGICAL ACTION**Pharmacodynamic properties:**

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 1 000 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 global and specific clotting tests are affected by rivaroxaban. Dose dependent inhibition of factor Xa activity was observed in humans.

Dose dependent but not dose-proportional inhibition of factor Xa activity has been 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 undergoing major orthopaedic surgery, the 5/95 percentiles for PT, 2 – 4 hours after 10 mg tablet intake (i.e. at the time of maximum effect), ranged from 13 to 25 seconds.

In patients receiving rivaroxaban for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin®) 2 – 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 – 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 HepTest® and activated partial thromboplastin time (aPTT) 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.

Pharmacokinetic properties:

Absorption and bioavailability:

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 to 4 hours after tablet intake.

The absolute bioavailability of rivaroxaban is 80 - 100 % for the 10 mg dose.

Administration of rivaroxaban 10 mg 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 “**DOSAGE AND DIRECTIONS FOR USE**”). Rivaroxaban pharmacokinetics for the 10 mg tablets is linear with no relevant undue accumulation beyond steady-state after multiple doses. Under fasting conditions, the oral bioavailability for the 20 mg tablet dose is 66 %. 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 are to be taken with food (see “**DOSAGE AND DIRECTIONS FOR USE**”). The oral bioavailability of rivaroxaban is reduced with increased doses.

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 litres.

Metabolism and elimination:

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

Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 and also 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 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. However, the half-life varies considerably between patients.

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 “**DOSAGE AND DIRECTIONS FOR USE**”).

Different weight categories:

Extremes in body weight (< 50 kg or > 120 kg had only a small influence on rivaroxaban plasma concentrations (less than 25 %) (see “**DOSAGE AND DIRECTIONS FOR USE**”). No dose adjustment is necessary.

Children and adolescents:

Safety and efficacy have not been established for children and adolescents below 18 years (see “**DOSAGE AND DIRECTIONS FOR USE**”).

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 contra-indicated in patients with any hepatic impairment which is associated with coagulopathy leading to a clinically relevant bleeding risk and in patients with Child-Pugh B or C hepatic impairment (see “**CONTRA-INDICATIONS**”).

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), given a single dose of 10 mg rivaroxaban, the rivaroxaban mean AUC was significantly increased by 2,3-fold compared to healthy volunteers, due to significantly impaired rivaroxaban clearance which indicates significant liver disease. Unbound AUC was increased 2,6-fold. There are no data in patients with severe hepatic impairment.

In this study the inhibition of factor Xa activity was increased by a factor of 2,6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2,1. 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. Patients with severe hepatic impairment were not included in this study. As this study was not conducted at steady state, no firm conclusion regarding safety in patients with moderate or severe hepatic impairment can be made (see “**CONTRA-INDICATIONS**”).

No data are available for Child Pugh C patients (see “**DOSAGE AND DIRECTIONS FOR USE**” and “**CONTRA-INDICATIONS**”).

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 \leq 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 “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**DOSAGE AND DIRECTIONS FOR USE**”).

Corresponding increases in pharmacodynamics effects were more pronounced (see “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**DOSAGE AND DIRECTIONS FOR USE**”).

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. Rivaroxaban should not be used in patients with creatinine clearance $<$ 15 ml/min (see “**CONTRA-INDICATIONS**”).

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance $<$ 30 to 15 ml/min) (see “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**DOSAGE AND DIRECTIONS FOR USE**”). Due to the underlying disease patients with severe renal impairment are at an increased risk of both thrombosis and bleeding.

INDICATIONS

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

Rivaroxaban, as in **RIVAXORED 10**, has not been studied in clinical trials in patients undergoing hip fracture surgery.

RIVAXORED 15 and **RIVAXORED 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).

CONTRA-INDICATIONS

RIVAXORED is contra-indicated in patients with:

- Hypersensitivity to rivaroxaban or to any of the tablet excipients of **RIVAXORED**.
- Clinically significant active bleeding from any body site (e.g. intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- 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.
- Any hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk including cirrhotic patients with Child-Pugh B and C (see **“Pharmacokinetic properties”**).
- Cirrhotic patients with Child-Pugh B and C hepatic impairment with or without coagulopathy.
- End stage renal impairment, creatinine clearance < 15 mL/min (see **“PHARMACOLOGICAL ACTION”**).
- Patients with prior stroke or transient ischaemic attacks.
- Pregnancy and lactation (See **“PREGNANCY AND LACTATION”**).
- Concomitant treatment is contra-indicated with any other anticoagulant, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc.), heparin derivatives (fondaparinux etc.), oral anticoagulants (warfarin and others)

except under the circumstances of switching therapy to or from RIVAROXABAN, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

- Persistently triple positive antiphospholipid syndrome (APS). [Triple positive = Test positive for all three antiphospholipid antibody tests – lupus anticoagulant, anti-cardiolipin antibodies and anti-beta 2 glycoprotein 1 antibodies].

WARNINGS AND SPECIAL PRECAUTIONS

The usual clotting tests such as INR/aPTT cannot be used for the therapeutic monitoring of RIVAXORED.

Patients with prosthetic valves:

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

Bleeding risk:

Patients taking **RIVAXORED** are to be carefully observed for signs of bleeding.

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

- Uncontrolled severe arterial hypertension
- Recent gastrointestinal ulcerations
- Intraspinal or intracerebral vascular abnormalities
- Recent brain, spinal or ophthalmological surgery
- Vascular retinopathy
- Bronchiectasis
- 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), acetylsalicylic acid (aspirin), platelet aggregation inhibitors, or other antithrombotics, or selective serotonin

reuptake inhibitors (SSRIs) and serotonin norepinephrine (noradrenaline) reuptake inhibitors (SNRIs) (see “**INTERACTIONS**”).

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see “**INTERACTIONS**”).

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

After treatment with **RIVAXORED 10** is initiated patients should be carefully monitored for signs of bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Surgery and interventions:

If an invasive procedure or surgical intervention is required, **RIVAXORED** 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.

RIVAXORED 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 “**Pharmacokinetic properties/metabolism and elimination**”).

Neuraxial (epidural/spinal) anaesthesia:

When neuraxial (epidural/spinal) anaesthesia or spinal puncture is employed, patients treated with **RIVAXORED** 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 punctures. Patients should be withdrawn at least 24 hours prior to any neuraxial procedures.

For the removal of an epidural catheter at least 24 hours should elapse after the last administration of **RIVAXORED**. Following removal of the catheter, at least 6 hours should

elapse before the next **RIVAXORED** dose is administered. If a traumatic puncture occurs, the administration of **RIVAXORED** should be delayed for 24 hours.

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.

Renal impairment:

RIVAXORED 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 “**INTERACTIONS**”).

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 **RIVAXORED** should be used with caution in patients with creatinine clearance < 30 to 15 ml/min.

Since no clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min), **RIVAXORED** should not be used in these patients (see “**CONTRA-INDICATIONS**”, “**DOSAGE AND DIRECTIONS FOR USE**”, “**Pharmacokinetic properties**” and “**Pharmacodynamic properties**”).

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

Concomitant medication:

The use of **RIVAXORED** is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These medicines are strong inhibitors of both CYP 3A4 and P-gp and therefore may increase the rivaroxaban plasma concentrations to a clinically relevant degree (2,6 fold on average) which may lead to an increased bleeding

risk (see “**INTERACTIONS**”).

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

Hip fracture surgery:

RIVAXORED has not been studied in clinical trials in patients undergoing hip fracture surgery.

Women of childbearing potential:

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

Elderly population :

Increasing age may increase haemorrhagic risk.

QTc prolongation:

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

Dermatological reactions:

Serious skin reactions, including Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, have been reported during post-marketing surveillance in association with the use of rivaroxaban, as in **RIVAXORED**. 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. **RIVAXORED** 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.

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

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

Patients with antiphospholipid syndrome:

Treatment of patients with established antiphospholipid syndrome (APS) is not recommended

as evidence regarding safety and efficacy, including the benefit/harm balance of **RIVAXORED** (and other 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 **RIVAXORED** is associated with an increased risk of recurrent arterial thrombotic events compared with treatment of these patients with warfarin, a vitamin K antagonist (see “**CONTRA-INDICATIONS**”). Prescribers should review whether continued/current treatment with **RIVAXORED** is still appropriate for APS patients. Where appropriate patients should be switched to a vitamin K antagonist.

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 “**SIDE-EFFECTS**”). Patients experiencing these adverse reactions should not drive or use machines.

Information about excipients:

RIVAXORED contains lactose. Patients with rare hereditary conditions of lactose or galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take **RIVAXORED**.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS

Pharmacokinetic interactions:

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP2J2) hepatic metabolism and renal excretion of the unchanged medicine, involving the P-glycoprotein (P-gp)/breast cancer resistance protein (BCRP) transporter systems (see “**Pharmacokinetic properties**”).

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 **RIVAXORED**:*

The concomitant use of **RIVAXORED** 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 “**WARNINGS AND SPECIAL PRECAUTIONS**”).

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, the use of **RIVAXORED** is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors (see “**WARNINGS AND SPECIAL PRECAUTIONS**”). These active substances are strong inhibitors of both CYP 3A4 and P-gp. 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 not considered clinically 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 not considered clinically relevant.

In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1,8-fold

increase in mean rivaroxaban AUC and 1,6-fold increase in C_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2,0-fold increase in mean rivaroxaban AUC and 1,6-fold increase in C_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment.

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 not considered clinically 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 “**Pharmacokinetic properties**”).

The concomitant use of **RIVAXORED** with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort (*Hypericum perforatum*)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP 3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

Pharmacodynamic interactions:

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants.

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 “**WARNINGS AND SPECIAL PRECAUTIONS**”).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (10 mg) and 500 mg naproxen or rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

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. The possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRI's or SNRIs due to their reported effect on platelets.

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 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 **RIVAXORED** (see “**DOSAGE AND DIRECTIONS FOR USE**”).

If it is desired to test the pharmacodynamics 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.

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 (aspirin).

Interactions with laboratory parameters:

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

PREGNANCY AND LACTATION

Pregnancy:

Animal data show that rivaroxaban crosses the placental barrier. Therefore the use of **RIVAXORED** is contra-indicated throughout pregnancy (see “**CONTRA-INDICATIONS**”).

Women of Childbearing Potential:

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

Lactation:

Rivaroxaban is secreted into breast milk. Mothers who are taking **RIVAXORED** should not breastfeed their infants (see “**CONTRA-INDICATIONS**”).

DOSAGE AND DIRECTIONS FOR USE

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

Method of administration:

Oral use.

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery of the lower limbs – Recommended dose and frequency of administration:

The recommended dose is one **RIVAXORED 10** tablet once daily.

RIVAXORED 10 may be taken with or without food.

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

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery of the lower limbs – Missed dose:

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

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery of the lower limbs – 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.

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery of the lower limbs – Additional information on special populations:

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery – Elderly (above 65 years), Gender, Body Weight or ethnic differences:

No dose adjustment is required for these patient populations.

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery – Children (up to 18 years of age):

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

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery – Patients with impaired liver function:

RIVAXORED 10 is contra-indicated in patients with moderate to severe hepatic impairment and in any patients with hepatic impairment associated with coagulopathy (see “**CONTRA-INDICATIONS**”).

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.

Prevention of venous thromboembolism (VTE) in major orthopaedic surgery – Patients with

impaired renal function:

No dose adjustment is required if **RIVAXORED 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 **RIVAXORED 10** must be used with caution in these patients (see “**WARNINGS AND SPECIAL PRECAUTIONS**”).

RIVAXORED 10 should not be used in patients with creatinine clearance < 15 ml/min (see “**CONTRA-INDICATIONS**”, “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**Pharmacokinetic properties**”).

SPAF – Recommended usual dose and frequency of administration:

The recommended dose is one **RIVAXORED 20** tablet once daily.

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

RIVAXORED 15 and **RIVAXORED 20** 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 **RIVAXORED 15** or **RIVAXORED 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 maximum daily dose is one **RIVAXORED 20** tablet (20 mg rivaroxaban).

SPAF – Additional information on special populations:

SPAF – Patients with hepatic impairment:

RIVAXORED 15 and **RIVAXORED 20** are contra-indicated in patients with moderate to severe hepatic impairment with or without coagulopathy (see “**CONTRA-INDICATIONS**”).

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 “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**Pharmacokinetic properties**”).

SPAF – Patients with renal impairment:

No dose adjustment is required if **RIVAXORED 20** is administered in patients with mild (creatinine clearance \leq 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 **RIVAXORED 15** tablet once daily.

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 **RIVAXORED** must be used with caution in these patients.

RIVAXORED 15 or **RIVAXORED 20** should not be used in patients with creatinine clearance $<$ 15 ml/min (see “**CONTRA-INDICATIONS**”, “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**Pharmacokinetic properties**”).

*SPAF – Converting from warfarin to **RIVAXORED 15** or **RIVAXORED 20**:*

Warfarin treatment should be stopped and **RIVAXORED 15** or **RIVAXORED 20** therapy should be initiated when the INR is \leq 3,0.

When converting patients from warfarin to **RIVAXORED 15** or **RIVAXORED 20**, INR values will be falsely elevated after the intake of **RIVAXORED 15** or **RIVAXORED 20**. The INR is not valid to measure the anticoagulant activity of **RIVAXORED 15** or **RIVAXORED 20**, and therefore should not be used (see “**INTERACTIONS**”).

*SPAF – Converting from **RIVAXORED 15** or **RIVAXORED 20** to warfarin:*

There is a potential for inadequate anticoagulation during the transition from **RIVAXORED 15** or **RIVAXORED 20** to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that **RIVAXORED 15** and **RIVAXORED 20** can contribute to an elevated INR.

In patients converting from **RIVAXORED 15** or **RIVAXORED 20** 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 **RIVAXORED 15** or **RIVAXORED 20** and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of **RIVAXORED 15** or **RIVAXORED 20**). Once **RIVAXORED 15** or **RIVAXORED 20** is discontinued INR testing may be done reliably 24 hours after the last dose (see “**INTERACTIONS**”).

*SPAF – Converting from parenteral anticoagulants to **RIVAXORED 15** or **RIVAXORED 20**:*

For patients currently receiving a parenteral anticoagulant, start **RIVAXORED 15** or **RIVAXORED 20**, 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 **RIVAXORED 15** or **RIVAXORED 20** to parenteral anticoagulants:*

Discontinue **RIVAXORED 15** or **RIVAXORED 20** and give the first dose of parenteral anticoagulant at the time that the next **RIVAXORED 15** or **RIVAXORED 20** 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 “**Pharmacokinetic properties**”).

Treatment and prevention of recurrent DVT and PE – Recommended usual dose and frequency of administration:

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

Following completion of at least 6 months treatment for DVT or PE, **RIVAXORED 20** once daily, re-assessment for continued therapy is recommended based on an individual assessment of the risk of recurrent DVT or PE against the risk of bleeding. **RIVAXORED**

treatment should not be discontinued in patients with recurrent DVT or PE.

RIVAXORED 15 and **RIVAXORED 20** tablets should be taken with food.

DVT and PE treatment – Duration of treatment:

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

Treatment and prevention of recurrent DVT and PE – Missed dose:

It is essential to adhere to the dosage schedule provided.

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

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

Treatment and prevention of recurrent DVT and PE – 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:

RIVAXORED 15 and **RIVAXORED 20** are contra-indicated in patients with moderate to severe hepatic impairment with or without coagulopathy (see “**CONTRA-INDICATIONS**”).

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 “**CONTRA-INDICATIONS**” and “**Pharmacokinetic properties**”).

DVT and PE treatment – Patients with renal impairment:

No dose adjustment is required if **RIVAXORED 15** and **RIVAXORED 20** is administered in patients with mild (creatinine clearance \leq 80 to 50 ml/min) or moderate (creatinine clearance $<$

50 to 30 ml/min) renal impairment (see “**Pharmacokinetic properties**”).

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 **RIVAXORED 15** and **RIVAXORED 20** must be used with caution in these patients.

RIVAXORED 15 and **RIVAXORED 20** should not be used in patients with creatinine clearance < 15 ml/min (see “**CONTRA-INDICATIONS**”, “**WARNINGS AND SPECIAL PRECAUTIONS**” and “**Pharmacokinetic properties**”).

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

Warfarin treatment should be stopped and **RIVAXORED 15** therapy should be initiated once the INR is $\leq 2,5$.

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

*DVT and PE treatment – Converting from **RIVAXORED 15** or **RIVAXORED 20** to warfarin:*

There is a potential for inadequate anticoagulation during the transition from **RIVAXORED 15** or **RIVAXORED 20** to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that **RIVAXORED 15** and **RIVAXORED 20** can contribute to an elevated INR.

In patients converting from **RIVAXORED 15** or **RIVAXORED 20** to warfarin, warfarin should be given concurrently until the INR is $\geq 2,0$. 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 **RIVAXORED 15** or **RIVAXORED 20** and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of **RIVAXORED 15** or **RIVAXORED 20**). Once **RIVAXORED 15** or **RIVAXORED 20** is discontinued INR testing may be done reliably 24 hours after the last dose (see “**INTERACTIONS**”).

*DVT and PE treatment – Converting from parenteral anticoagulants to **RIVAXORED 15**:*

For patients currently receiving a parenteral anticoagulant, start **RIVAXORED 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 **RIVAXORED 15** or **RIVAXORED 20** to parenteral anticoagulants:*

Discontinue **RIVAXORED 15** or **RIVAXORED 20** and give the first dose of parenteral anticoagulant at the time that the next **RIVAXORED 15** or **RIVAXORED 20** 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**”).

SIDE-EFFECTS

Summary of the safety profile:

RIVAXORED is associated with an increased risk of occult or overt bleeding from any organ and tissue 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 “**WARNINGS AND SPECIAL PRECAUTIONS**”).

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 “**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**”).

Haemorrhagic complications may present as dizziness, weakness, paleness, 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 **RIVAXORED**. Therefore, the possibility of a haemorrhage should be considered in evaluating the condition in any anticoagulated patient.

All treatment-emergent adverse reactions reported in patients in phase III studies with rivaroxaban, as in RIVAXORED:

Blood and the lymphatic system disorders:

Frequent:

Bleeding, anaemia (incl. respective laboratory parameters)

Less frequent:

Thrombocythaemia (incl. platelet count increased)^A

Immune system disorders:

Less frequent:

Allergic reaction, allergic dermatitis

Nervous system disorders:

Frequent:

Dizziness, headache

Less frequent:

Cerebral and intracranial haemorrhage, syncope

Eye disorders:

Frequent:

Eye haemorrhage (incl. conjunctival haemorrhage)

Cardiac disorders:

Less frequent:

Tachycardia

Vascular disorders:

Frequent:

Hypotension, haematoma

Respiratory, thoracic and mediastinal disorders:

Frequent:

Epistaxis, haemoptysis

Gastrointestinal disorders:

Frequent:

Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage),
gastrointestinal and abdominal pains, dyspepsia, nausea, constipation^A, diarrhoea, vomiting^A

Less frequent:

Dry mouth

Hepato-biliary disorders:

Less frequent:

Abnormal hepatic function, hepatic impairment, jaundice

Skin and subcutaneous tissue disorders:

Frequent:

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

Less frequent:

Urticaria

Musculoskeletal, connective tissue and bone disorders:

Frequent:

Pain in extremity^A

Less frequent:

Haemarthrosis, muscle haemorrhage

Frequency not known:

Compartment syndrome secondary to a bleeding

Renal and urinary disorders:

Frequent:

Urogenital tract haemorrhage (incl. haematuria and menorrhagia^B), renal impairment (incl.
blood creatinine increased, blood urea increased)^A

Frequency not known:

Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion

General disorders and administration site conditions:

Frequent:

Fever^A, peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)

Less frequent:

Feeling unwell (incl. malaise), localised oedema^A

Investigations:

Frequent:

Increase in transaminases

Less frequent:

Increased bilirubin, increased blood alkaline phosphatase^A, increased LDH^A, increased lipase^A, increased amylase^A, increased GGT^A, increased conjugated bilirubin (with or without concomitant increase of ALT)

Injury, poisoning and postprocedural complications:

Frequent:

Post-procedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion

Less frequent:

Wound secretion^A, vascular pseudoaneurysm^C

A: Observed after major orthopaedic surgery of the lower limbs

B: Observed in VTE treatment as very common in women < 55 years

C: Observed as uncommon in prevention therapy in ACS (following percutaneous intervention)

Post-marketing observations:

Immune system disorders:

Frequency not known:

Angioedema and allergic oedema

Hepato-biliary disorders:

Frequency not known:

Cholestasis, hepatitis (including hepatocellular injury)

Blood and the lymphatic system disorders:

Frequency not known:

Thrombocytopenia

Skin and subcutaneous tissue disorders:

Frequency not known:

Stevens-Johnson syndrome/toxic epidermal necrolysis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

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

The use of activated charcoal to reduce absorption in case of **RIVAXORED** 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 rivaroxaban is not expected to be dialysable.

Management of bleeding:

Should a bleeding complication arise in a patient receiving **RIVAXORED**, the next administration should be delayed or treatment should be discontinued as appropriate.

Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualised according to the location and severity of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving **RIVAXORED**.

Vitamin K and protamine sulphate are not expected to affect the anticoagulant activity of **RIVAXORED**.

There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving **RIVAXORED**. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving **RIVAXORED**.

IDENTIFICATION

RIVAXORED 10: Light pink coloured, round, biconvex film-coated tablets, engraved with '10' on one side and plain on other side.

RIVAXORED 15: Red coloured, round, biconvex film-coated tablets, engraved with '15' on one side and plain on other side.

RIVAXORED 20: Dark red coloured, round, biconvex film-coated tablets, engraved with '20' on one side and plain on other side.

PRESENTATION

The tablets are packed in clear PVC/PVdC film / silver coloured aluminium foil blister strips. Each blister strip contains 10 or 14 tablets. The blister strip/s are packed into a unit carton.

RIVAXORED 10, 15, 20: Blister packs of 28 tablets (2 blister strips of 14 tablets each) or 30 tablets (3 blister strips of 10 tablets each).

STORAGE INSTRUCTIONS

Store at or below 25 °C. Keep blister strips in the original carton until use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

RIVAXORED 10: 52/8.2/0179

RIVAXORED 15: 52/8.2/0180

RIVAXORED 20: 52/8.2/0181

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF
REGISTRATION**

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DATE OF PUBLICATION OF THE PACKAGE INSERT

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