1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEBIVOPEN 10, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg rivaroxaban.

Contains sugar: 95,6 mg lactose monohydrate per tablet

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

A pink, round, biconvex film-coated tablet, engraved with “10” on one side, plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

4.2 Posology and method of administration

Posology

The recommended dose for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery of the lower limbs is 10 mg once daily.

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

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

Duration of treatment

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

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

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

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE

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

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). In patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE a longer duration of therapy should be considered.

A 10 mg once daily dose is recommended when extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE). A dose of 20 mg NEBIVOPEN once daily should be considered in patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with NEBIVOPEN 10 once daily.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4).

	Time period	Dosing schedule	Total daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg
Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take NEBIVOPEN immediately to ensure intake of 30 mg NEBIVOPEN per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take NEBIVOPEN 10 immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to NEBIVOPEN10

VKA treatment should be stopped and NEBIVOPEN 10 therapy should be initiated once the INR is ≤ 2.5 for patients treated for DVT, PE and prevention of recurrence.

When converting patients from VKAs to NEBIVOPEN 10, International Normalised Ratio (INR) values will be falsely elevated after the intake of NEBIVOPEN 10. The INR is not valid to measure the anticoagulant activity of NEBIVOPEN 10, and therefore should not be used (see section 4.5).

Converting from NEBIVOPEN 10 to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from NEBIVOPEN 10 to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that NEBIVOPEN 10 can contribute to an elevated INR.

In patients converting from NEBIVOPEN 10 to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both NEBIVOPEN 10 and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of NEBIVOPEN 10. Once NEBIVOPEN is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

Converting from parenteral anticoagulants to NEBIVOPEN 10

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start NEBIVOPEN 10, 0 to 2 hours before the time that the next scheduled administration of the parenteral medicine (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

Converting from NEBIVOPEN 10 to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next NEBIVOPEN 10 dose would be taken.

Special patient populations

Elderly (above 65 years), gender and body weight

No dose adjustment is required for these patient populations.

Patients with impaired liver function

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

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

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

Patients with impaired renal function

No dose adjustment is required if NEBIVOPEN 10 is administered in patients with mild (creatinine clearance 50 - 80 ml/min) or moderate (creatinine clearance 30 - 49 ml/min) renal impairment.

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore NEBIVOPEN 10 has to be used with caution in these patients (see section 4.4).

Paediatric population

Children (up to 18 years of age)

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

Method of administration

For oral use.

NEBIVOPEN 10 may be taken with or without food.

NEBIVOPEN 10 tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally for patients who are unable to swallow whole tablets.

The crushed NEBIVOPEN 10 tablet may also be administered through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be given in a small amount of water via a gastric tube after which it should be flushed with water (see section 5.2).

4.3 Contraindications

- Hypersensitivity to rivaroxaban or any excipient of NEBIVOPEN 10.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding)
- 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 considerable 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).
- Significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 5.2).
- Pregnancy and lactation (see section 4.6).
- Patients with persistent triple positive antiphospholipid syndrome (APS).

4.4 Special warnings and precautions for use

WARNING: (A) PREMATURE DISCONTINUATION OF NEBIVOPEN INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HAEMATOMA

A. Premature discontinuation of NEBIVOPEN increase the risk of thrombotic events:

Premature discontinuation of any oral anticoagulant, including NEBIVOPEN, increases the risk of thrombotic events. If anticoagulation with NEBIVOPEN is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [*see Posology and method of administration (4.2), and Special warnings and precautions (4.4.)*].

B. Spinal/epidural haematoma:

Epidural or spinal hematomas have occurred in patients treated with NEBIVOPEN who are receiving neuraxial anaesthesia or undergoing spinal puncture. These haematomas may result in long-term or permanent paralysis.

Consider these risks when scheduling patients for spinal procedures.

Factors that can increase the risk of developing epidural or spinal haematomas in these patients include:

- **Use of indwelling epidural catheters**
- **Concomitant use of other medicines that affect haemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **History of traumatic or repeated epidural or spinal punctures**
- **History of spinal deformity or spinal surgery**
- **Optimal timing between the administration of NEBIVOPEN and neuraxial procedures is not known *[see Special warnings and precautions (4.4) and Undesirable effects (4.8)].***

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Special warnings and precautions (4.4)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *(see Special warnings and precautions (4.4)*

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

NEBIVOPEN 10 like other antithrombotics 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
- other gastrointestinal disease, without active ulceration, that may potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- recent intracranial or intracerebral haemorrhage
- shortly after brain, spinal or opthalmological surgery.
- bronchiectasis or history of pulmonary bleeding.

Haemorrhagic risk

Patients taking NEBIVOPEN 10 have to be carefully observed for signs of bleeding. It should be used with caution in conditions with increased risk of haemorrhage. NEBIVOPEN 10 administration should be discontinued if severe haemorrhage occurs (see section 4.9).

Mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito-urinary (including abnormal vaginal or increased menstrual bleeding)) and anaemia may be seen more frequently during long-term treatment with NEBIVOPEN compared with vitamin K antagonist (VKA) treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Several sub-groups of patients, as detailed in this section, are at increased risk of bleeding. These patients should be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving NEBIVOPEN for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

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

Bleeding during antithrombotic treatment may unmask underlying yet unknown malignancy, in particular in the gastrointestinal or genitourinary tract. Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumor location, antineoplastic therapy and stage of disease.

Renal impairment

In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1,6-fold on average) which may lead to an increased bleeding risk.

NEBIVOPEN should be used with caution in patients with creatinine clearance 15 – 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). In patients with moderate renal impairment (creatinine clearance 30 – 49 ml/min) concomitantly receiving other medicines which increase rivaroxaban plasma concentrations NEBIVOPEN 10 should be used with caution (see section 4.5).

Interaction with other medicines

NEBIVOPEN 10 must be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2,6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

Patients should be carefully monitored for signs of bleeding complications after treatment initiation. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

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

No QTc prolonging effect was observed with NEBIVOPEN 10.

Patients with prosthetic valves

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

NEBIVOPEN have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that NEBIVOPEN provides adequate anticoagulation in this patient population. Treatment with NEBIVOPEN is not recommended for these patients.

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including rivaroxaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery

Rivaroxaban has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Haemodynamically unstable pulmonary embolism (PE) patients or patients who require thrombolysis or pulmonary embolectomy

NEBIVOPEN 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 NEBIVOPEN have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines for prevention of thromboembolic

complications are at risk of developing an epidural or spinal haematoma which may result in long-term 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 doctor should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

To reduce the potential risk of bleeding associated with the concurrent use of NEBIVOPEN 10 and neuraxial (epidural/spinal) anaesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low (see section 5.2)***.***

At least 18 hours should elapse after the last administration of NEBIVOPEN 10 before removal of an epidural catheter.

Following removal of the catheter, at least 6 hours should elapse before the next NEBIVOPEN 10 dose is administered.

If a traumatic puncture occurs the administration of NEBIVOPEN 10 should be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery:

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

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

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

Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of rivaroxaban (see section 4.8). Patients appear to be at highest risk for these reactions early during therapy: the onset of the reaction occurring in the most cases within the first weeks of treatment. NEBIVOPEN 10 should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

NEBIVOPEN 10 contains lactose monohydrate (see section 6.1). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take NEBIVOPEN 10.

Lactose monohydrate may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interactions with other medicines and other forms of interactions

Pharmacokinetic interactions

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

CYP Inhibition

CYP 3A4 or any other major CYP isoforms are not inhibited by rivaroxaban.

CYP Induction

CYP 3A4 or any other major CYP isoforms are not induced by rivaroxaban.

Effects on NEBIVOPEN 10

The concomitant use of NEBIVOPEN 10 with strong CYP 3A4 and P gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure.

CYP3A4 and P-gp inhibitors

Co-administration of NEBIVOPEN 10 with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) leads 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 NEBIVOPEN 10 is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, leads to a 1,5-fold increase in mean rivaroxaban AUC and a 1,4-fold increase in C_{max}. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).

Erythromycin, (500 mg three times a day) which inhibits CYP3A4 and P-gp moderately, leads to a 1,3-fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant.

In patients with mild renal impairment erythromycin (500 mg three times a day) leads to a 1,8-fold increase in mean rivaroxaban AUC and 1,6-fold increase in C_{max} when compared to patients with normal renal function.

In patients with moderate renal impairment, erythromycin leads to a 2,0-fold increase in mean rivaroxaban AUC and 1,6-fold increase in C_{max} when compared to patients 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, leads to a 1,4-fold increase in mean rivaroxaban AUC and a 1,3-fold increase in mean C_{max}. This increase is not considered clinically relevant. (For patients with renal impairment: see section 4.4).

In the absence of clinical data on concomitant use of dronedarone, co-administration with rivaroxaban should be avoided.

Pharmacodynamic interactions

Anticoagulants

After combined administration of enoxaparin with rivaroxaban an additive effect on anti-factor Xa activity was observed, without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk, care is to be taken if patients are treated concomitantly with any other anticoagulants (see section 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time has been observed after concomitant administration of rivaroxaban and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response (see section 4.4).

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

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) does not show a pharmacokinetic interaction with NEBIVOPEN 10 but a relevant increase in bleeding time is observed, which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels (see section 4.4).

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).

Selective serotonin reuptake inhibitors (SSRIs)/Serotonin and norepinephrine reuptake inhibitors (SNRIs)

Patients may possibly be at increased risk of bleeding in case of concomitant use with selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), due to their reported effect on platelets. Higher rates of major or non-major clinically relevant bleeding has been observed with these medicines.

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2,0 to 3,0) to NEBIVOPEN 10, or from NEBIVOPEN 10 to warfarin (INR 2,0 to 3,0), increases 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 has been additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period; anti-factor Xa activity, PiCT, and Heptest may be used as these tests are 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 endogenous thrombin potential (ETP)) may reflect only the effect of rivaroxaban as in NEBIVOPEN 10.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement may 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 as in NEBIVOPEN 10.

CYP3A4 inducers

Co-administration of NEBIVOPEN 10 with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of NEBIVOPEN 10 with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort *(Hypericum perforatum)*) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be administered with caution.

Other concomitant therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions are observed when rivaroxaban, as in NEBIVOPEN 10 is co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Co-administration of the H_2 receptor antagonist ranitidine and antacid aluminium hydroxide / magnesium hydroxide did not affect rivaroxaban bioavailability and pharmacokinetics.

No clinically relevant interaction with food was observed (see section 4.2).

Interactions with Laboratory parameters

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

4.6 Fertility, pregnancy and lactation

Safety and/or efficacy has not been established.

Women of childbearing potential

NEBIVOPEN 10 should be used in women of childbearing potential only with effective contraception.

Pregnancy

NEBIVOPEN 10 is contraindicated in pregnancy (see section 4.3).

In rats and rabbits, rivaroxaban, as in NEBIVOPEN 10, showed pronounced maternal toxicity with placental changes related to the pharmacological mode of action (e.g., haemorrhagic complications) leading to reproductive toxicity. No primary teratogenic potential was identified. Animal data show that rivaroxaban crosses the placental barrier.

Breastfeeding

Safety and efficacy of NEBIVOPEN 10 have not been established in nursing mothers.

In rats, rivaroxaban is secreted into breast milk. Therefore NEBIVOPEN 10 is contraindicated during breastfeeding (see section 4.3) and may only be administered after breastfeeding is discontinued.

Fertility

No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen (see section 5.3).

4.7 Effects on ability to drive and use machines

Adverse reactions like syncope and dizziness have been reported with the use of NEBIVOPEN 10 (see section 4.8). Patients experiencing these side effects should not drive or use machines.

4.8 Undesirable effects

The following side-effects can occur:

Blood and lymphatic system disorders

Frequent: Anaemia (including respective laboratory parameters), bleedings (see section 4.4)

Less frequent: Thrombocythemia (incl. increased platelet count)

Immune system disorders

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

Nervous system disorders

Frequent: Dizziness, headache

Less frequent: Cerebral and intracranial haemorrhage, syncope (including loss of consciousness)

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: 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 (including rare cases of generalised urticaria), Stevens-Johnson syndrome/Toxic Epidermal Necrolysis, DRESS syndrome

Musculoskeletal and connective tissue disorders

Frequent: Pain in extremity[A]

Less frequent: Haemarthrosis, muscle haemorrhage

Frequency unknown: Compartment syndrome secondary to a bleeding

Renal and urinary disorders

Frequent: Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. increased blood creatinine, increased blood urea)

Frequency unknown: 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 LDH[A], increased lipase[A], increased amylase[A], increased bilirubin, increased blood alkaline phosphatase, increased GGT[A], bilirubin conjugated increased (with or without concomitant increase of ALT

Injury, poisoning and procedural complications

Frequent: Post-procedural haemorrhage (incl. post-operative anaemia, and wound haemorrhage), contusion

Less frequent: Wound secretion, vascular pseudoaneurysm

[A] observed after major orthopedic 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)

Description of selected adverse reactions

NEBIVOPEN may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in post haemorrhagic anaemia, due to the pharmacological mode of action. Certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or on concomitant medication affecting haemostasis may experience an increased risk of bleedings (see section Special warnings and precautions for use). The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section Overdose / Management of Bleeding).

Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischemia 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 NEBIVOPEN. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post marketing observations

The following adverse reactions have been reported post-marketing in temporal association with the use of NEBIVOPEN. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.

Immune system disorders: Angioedema and allergic oedema.

Hepatobiliary disorders: Cholestasis, Hepatitis (including hepatocellular injury).

Blood and lymphatic system disorders: Thrombocytopenia.

Reporting of suspected adverse reactions

Reporting of 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

Symptoms

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

In case of overdose, observe your patient carefully for bleeding complications or other adverse reactions (see section 'Management of bleeding').

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

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

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. 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 NEBIVOPEN 10, the next dose should be delayed, or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage.

Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific pro-coagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered.

However, there is very limited clinical experience with the use of these products in individuals receiving NEBIVOPEN 10.

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of NEBIVOPEN 10. There is limited experience with tranexamic acid and no experience with

aminocaproic acid and aprotinin in individuals receiving NEBIVOPEN 10. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving NEBIVOPEN 10.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

A 8.2 Anticoagulants

Mechanism of action

Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability.

Activation of Factor X to Factor Xa via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation.

Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependant inhibition of factor FXa activity was observed in humans.

Pharmacodynamic effects

Dose dependent inhibition of factor Xa activity was observed in humans.

Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0,98) if Neoplastin® is used for the assay.

Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalised Ratio) is only calibrated and validated for warfarin and cannot be used for any other anticoagulant.

In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT, 2 to 4 hours after tablet intake (i.e. at the time of maximum effect), ranged from 13 to 25 seconds.

The activated partial thromboplastin 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.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban levels can be measured by calibrated quantitative anti-factor Xa tests (see section 5.2).

5.2 Pharmacokinetic properties

Absorption

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

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 – 100 %) irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. Rivaroxaban 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily.

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

Distribution

Plasma protein binding in humans is high (approximately 92 to 95 %), with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litre.

Biotransformation and elimination

Rivaroxaban is eliminated by metabolic degradation (approximately ⅔ of the administered dose) and by direct renal excretion of unchanged compound (approximately ⅓). Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 and (CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Elimination of rivaroxaban and metabolites occurs via both renal and faecal routes.

Approximately 66 % of a rivaroxaban dose is eliminated via the kidneys, with 30 - 40 % excreted as unchanged medicine, in the urine via both glomerular filtration and active renal secretion.

Rivaroxaban is 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 may be classified as a low-clearance medicine. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

There were no clinically relevant differences in pharmacokinetics between male and female patients.

Elderly patients (above 65 years)

Elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1,5-fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary (see section 4.2).

Weight categories

Extremes in body weight (< 50 kg versus > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary (see section 4.2).

Children (up to 18 years of age)

No data is available for this patient population.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibit only minor changes in rivaroxaban pharmacokinetics (1,2-fold increase in rivaroxaban AUC on average). In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC is significantly increased, by 2,3-fold compared to healthy persons. Unbound AUC was increased 2,6 fold. The inhibition of Factor Xa activity is increased by a factor of 2,6 compared with healthy persons; prolongation of PT is similarly increased, by a factor of 2,1.

The global clotting test PT assesses the extrinsic pathway (coagulation Factors VII, X, V, II, I), of which Factors II, VII, and X are synthesised in the liver. The elevated PT at baseline and a significantly altered sensitivity in anticoagulant activity towards rivaroxaban plasma exposure (increase in slope for PT / rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients classified as Child Pugh B indicate the decreased ability of the liver to synthesise coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group. Therefore, rivaroxaban is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 4.3).

No data are available for Child Pugh C patients (see section 4.2 and 4.3).

Renal impairment

There is 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 50-80 ml/min), moderate (creatinine clearance 30-49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) are 1,4; 1,5 and 1,6-fold increased respectively, as compared to healthy persons (see sections 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects are more pronounced (see sections 4.2 and 4.4).

In individuals with mild, moderate or severe renal impairment the overall inhibition of factor Xa activity is increased by a factor of 1,5; 1,9 and 2,0 respectively, as compared to healthy volunteers; prolongation of PT is similarly increased by a factor of 1,3; 2,2 and 2,4 respectively.

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. Rivaroxaban is to be used with caution in patients with severe renal impairment (see sections 4.2 and 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, microcrystalline cellulose, sodium lauryl sulphate, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in the original package.

Do not remove the blisters from the carton until required for use.

6.5 Nature and contents of container

The film-coated tablets are packed in PVC/aluminium foil blisters strips. The blister strips are packed in cartons containing 10, 14, 28, 30, 42, 98, or 100 tablets.

Not all packing sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands drive

Woodmead

2191

8 REGISTRATION NUMBER

53/8.2/0623

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

14 June 2022

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