1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEBIVOPEN 2,5, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2,5 mg rivaroxaban.

Contains sugar: 23,9 mg lactose monohydrate per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NEBIVOPEN 2,5 co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (see sections 4.3 and 4.4).

NEBIVOPEN 2,5 co-administered with aspirin, is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

4.2 Posology and method of administration

Posology

The recommended dose is 2,5 mg twice daily.

- **ACS**

Patients taking NEBIVOPEN 2,5 twice daily should also take a daily dose of 75 - 100 mg aspirin or a daily dose of 75 - 100 mg aspirin in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. Extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited.

Treatment with NEBIVOPEN 2,5 should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

- **CAD/PAD**

Patients taking NEBIVOPEN 2,5 twice daily should also take a daily dose of 75 - 100 mg aspirin.

Duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events versus the bleeding risks.

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of NEBIVOPEN 2,5 twice daily should be evaluated depending on the type

of event or procedure and antiplatelet regimen. Safety and efficacy of NEBIVOPEN 2,5 twice daily in combination with aspirin plus clopidogrel/ticlopidine has only been studied in patients with recent ACS (see section 4.1). No clinical data are available for dual antiplatelet therapy in combination with NEBIVOPEN 2,5 twice daily in patients with CAD/PAD (see sections 4.4).

If a dose is missed the patient should continue with the regular dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

Converting from Vitamin K Antagonists (VKA) to NEBIVOPEN

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

Converting from NEBIVOPEN to Vitamin K antagonists (VKA)

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

In patients converting from NEBIVOPEN 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 and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of NEBIVOPEN. 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

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

Converting from NEBIVOPEN to parenteral anticoagulants

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

Special populations

Renal impairment

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased in this patient population. Therefore, NEBIVOPEN 2,5 is to be used with caution in these patients. NEBIVOPEN 2,5 use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).
No dose adjustment is necessary in patients with mild (creatinine clearance 50 - 80 ml/min) or moderate (creatinine clearance 30 - 49 ml/min) renal impairment (see section 5.2).

Hepatic impairment

NEBIVOPEN 2,5 is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see sections 4.3 and 5.2).

Elderly population

No dose adjustment (see sections 4.4 and 5.2).

The risk of bleeding increases with increasing age (see section 4.4).

Body weight and gender

No dose adjustment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of NEBIVOPEN 2,5 have not been established in children up to 18 years of age. No clinical data are available. Therefore, NEBIVOPEN 2,5 is not recommended for use in children below 18 years of age.

Method of administration

For oral use.

NEBIVOPEN 2,5 may be taken with or without food (see sections 4.5 and 5.2).

NEBIVOPEN 2,5 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 2,5 tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. The crushed tablet should be administered 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 to any excipient of NEBIVOPEN 2,5.
- Clinically significant active 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 high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).
- Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).
- Concomitant treatment of CAD/PAD with aspirin in patients with previous haemorrhagic or lacunar (ischaemic) stroke, or any stroke within a month (see section 4.4).
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child-Pugh class B and class C (see section 5.2).
- Renally impaired patients with creatinine clearance < 15 ml/min.
- Patients with persistent triple positive antiphospholipid syndrome (APS).
- Pregnancy and breastfeeding (see section 4.6).

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), 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 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)*

In patients with ACS, efficacy and safety of NEBIVOPEN 2,5 have been investigated in combination with the antiplatelet medicines, aspirin alone or aspirin plus clopidogrel/ticlopidine. Treatment in combination with other antiplatelet medicines, e.g. prasugrel or ticagrelor, has not been studied and is not recommended. In patients at high risk of ischaemic events with CAD/PAD, efficacy and safety of NEBIVOPEN 2,5 have only been investigated in combination with aspirin.
Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Haemorrhagic risk

Patients taking NEBIVOPEN have to be carefully observed for signs of bleeding. NEBIVOPEN should be used with caution in conditions with increased risk of haemorrhage. NEBIVOPEN 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 on top of single or dual anti-platelet therapy. 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.

Several sub-groups of patients, as detailed in this section, are at increased risk of bleeding. Therefore, the use of NEBIVOPEN in combination with dual antiplatelet therapy in patients at known

increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition, these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after treatment initiation (see section 4.8).
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban 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 inform clinical decisions, e.g. overdose and emergency surgery (see section 5.2).

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 is to 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 is to be used with caution (see section 4.5).

Interaction with other medicines

NEBIVOPEN 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).

Care is to be taken if patients are treated concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), fibrinolytic therapy. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).
Patients on treatment with NEBIVOPEN and aspirin or with NEBIVOPEN and aspirin plus clopidogrel/ticlopidine should only receive concomitant treatment with NSAIDs if the benefit outweighs the bleeding risk.

Other haemorrhagic risk factors

NEBIVOPEN 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
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding (haemoptysis)

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.

NEBIVOPEN should be used with caution in patients with ACS and CAD/PAD:

- ≥ 75 years of age if co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine. The benefit-risk of the treatment should be individually assessed on a regular basis.
- with lower body weight (< 60 kg) if co-administered with aspirin alone or with aspirin plus clopidogrel or ticlopidine.
- patients with CAD with severe symptomatic heart failure.

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

Rivaroxaban (and direct acting oral anticoagulants (DOACs) with the same mechanism of action) is not recommended for treatment of patients with established antiphospholipid syndrome (APS). There is some evidence that treatment of persistently triple positive APS patients with rivaroxaban could be associated with an increased risk or recurrent arterial thrombotic events compared with treatment of these patients with warfarin, a vitamin K antagonist (see section 4.3).

Patients with prior stroke and/or transient ischaemic accident (TIA)

Patients with ACS

NEBIVOPEN 2,5 is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (see section 4.3). Limited efficacy data available for these patient population indicate no benefit from treatment.

Patients with CAD/PAD

No clinical data is available for CAD/PAD patients with previous haemorrhagic or lacunar stroke, or an ischaemic, non-lacunar (ischaemic) stroke with in the previous month (see section 4.3).

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which may result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of NEBIVOPEN 2,5 with aspirin alone or with aspirin plus clopidogrel or ticlopidine in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of NEBIVOPEN 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). However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Platelet aggregation inhibitors should be discontinued as suggested by the manufacturer's prescribing information.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, NEBIVOPEN 2,5 should be stopped at least 12 hours before the intervention, if possible and based on the clinical judgement of the physician. If a patient is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

NEBIVOPEN 2,5 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 2,5 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 2,5 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 2,5.

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of NEBIVOPEN with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6-fold / 2,5-fold increase in mean rivaroxaban AUC and a 1.7-fold / 1.6-fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of NEBIVOPEN 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 in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, leads to a 1.3-fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant in most patients but can be potentially significant in high-risk patients. 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 in most patients but can be potentially significant in high risk patients. (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.

Anticoagulants

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.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

Non steroidal anti-inflammatory drugs (NSAIDs)/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg aspirin.
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 time was observed, which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.
Care is to be taken if patients are treated concomitantly with NSAIDs (including aspirin 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 SSRIs or 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 (20 mg) or from NEBIVOPEN (20 mg) 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, antifactor 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 ETP) may reflect only the effect of rivaroxaban as in NEBIVOPEN 2,5.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban as in NEBIVOPEN 2,5.

CYP3A4 inducers

Co-administration of NEBIVOPEN 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 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 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.
No clinically relevant interaction with food was observed (see section 4.2).

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban as in NEBIVOPEN 2,5 (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

NEBIVOPEN 2,5 is contraindicated during pregnancy (see section 4.3)
Animal studies show potential reproductive toxicity, an intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta.

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban, as in NEBIVOPEN 2,5.

Breastfeeding

Safety and efficacy of NEBIVOPEN 2,5 have not been established in nursing mothers. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, NEBIVOPEN 2,5 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.

4.7 Effects on ability to drive and use machines

Adverse reactions like syncope and dizziness have been reported with the use of NEBIVOPEN 2,5 (see section 4.8). Patients experiencing these adverse reactions 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)

Less frequent: Thrombocytosis (including platelet count increased)[A], thrombocytopenia

Immune system disorders

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

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 (including rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]

Less frequent: Dry mouth

Hepatobiliary disorders

Frequent: Increase in transaminases

Less frequent: Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A], jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), Cholestasis, Hepatitis (including hepatocellular injury)

Skin and subcutaneous tissue disorders

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

Less frequent: 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 (incuding. blood creatinine increased, blood urea increased)

Frequency unknown: Renal failure/acute renal failure secondary to a bleeding sufficient to cause

hypoperfusion

General disorders and administration site conditions

Frequent: Fever[A], peripheral oedema, decreased general strength and energy (including fatigue and asthenia)

Less frequent: Feeling unwell (including malaise), localised oedema[A]

Investigations

Less frequent: Increased LDHA, increased lipase[A],

increased amylase[A]

Injury, poisoning and procedural complications

Frequent: Post-procedural haemorrhage (including post-operative anaemia, and wound haemorrhage), contusion, wound secretion[A]

Less frequent: Vascular pseudoaneurysm[C]

[A] observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery

[B] observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

[C] observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention)

Description of selected adverse reactions

NEBIVOPEN may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia, due to the pharmacological mode of action. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 Management of bleeding).

Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases, as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for NEBIVOPEN 2,5. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

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.

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 2,5, 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, administration of a specific procoagulant reversal medicine 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 medicines in individuals receiving NEBIVOPEN 2,5. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of NEBIVOPEN 2,5. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving NEBIVOPEN 2,5. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving NEBIVOPEN 2,5.

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.

Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no direct effects on platelets aggregation have been demonstrated. Indirectly, rivaroxaban inhibits platelet aggregation induced by thrombin.

Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are prolonged by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay.

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

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult patients (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor Prothrombin complex concentrate (PCC) (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC (see section 4.9).

The (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban.

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

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine.

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 2,5 mg dose. Rivaroxaban 2,5 mg tablets can be taken with or without food.

Rivaroxaban pharmacokinetics is are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. 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 Vss being approximately 50 litres.

Biotransformation and elimination

Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose) and by direct renal excretion of unchanged compound (approximately 1/3). Rivaroxaban is metabolised via CYP3A4, CYP2J2 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 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.

Special populations

Gender

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

Elderly population

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).

Different weight categories

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

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years.

Hepatic impairment

Cirrhotic patients with mild hepatic impairment (classified as Child-Pugh class A) exhibited 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 class B), rivaroxaban mean total AUC was significantly increased by 2.3-fold compared to healthy persons. Unbound AUC was increased 2.6-fold.

The inhibition of factor Xa activity was increased by a factor of 2.6 compared to healthy persons; prolongation of PT was similarly increased by a factor of 2.1. Therefore, rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child-Pugh class B and class C (see section 4.3).

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements.

In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6-fold respectively, as compared to healthy persons (see sections 4.2 and 4.4).

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

In individuals with mild, moderate and 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 was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see section 4.4).

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 yellow.

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

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands drive

Woodmead

2191

8. REGISTRATION NUMBER

53/8.2/0622

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10. DATE OF REVISION OF THE TEXT

14 June 2022

ZA_NEBI2.5TAB_2206_00