1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

NEBIVOPEN 15, film-coated tablets

NEBIVOPEN 20, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 15 mg or 20 mg rivaroxaban.

Contains sugar:

NEBIVOPEN 15: 16,32 mg lactose monohydrate per tablet

NEBIVOPEN 20: 21,76 mg lactose monohydrate per tablet

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

NEBIVOPEN 15: A red, round, biconvex film-coated tablet, engraved with “15” on one side, plain on the other.

NEBIVOPEN 20: A brown-red, round, biconvex film-coated tablet, engraved with “20” on one side, plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NEBIVOPEN 15 and 20 are indicated for:

- the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF)
- treatment of deep venous thrombosis (DVT) and for the prevention of recurrent DVT and pulmonary embolism (PE)
- treatment of PE and for the prevention of recurrent PE and DVT.

4.2 Posology and method of administration

There is no need for monitoring of coagulation parameters during treatment with NEBIVOPEN 15 and 20.

SPAF - Posology

Stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (SPAF):

The recommended dose is one NEBIVOPEN 20 once daily.

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

If a dose is missed, the patient should take NEBIVOPEN 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.

The maximum daily dose is one NEBIVOPEN 20.

SPAF – Special populations

SPAF - patients with hepatic impairment:

NEBIVOPEN 15 and 20 are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

SPAF - patients with renal impairment:

No dose adjustment is required if NEBIVOPEN 20 is administered in patients with mild (creatinine clearance < 80 to 50 ml/min) renal impairment. For patients with moderate (creatinine clearance < 50 to 30 ml/min) renal impairment the recommended dose is one NEBIVOPEN 15, once daily.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore, NEBIVOPEN 15 should be used with caution in these patients.

Use of NEBIVOPEN 15 or NEBIVOPEN 20 is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

SPAF - Converting from warfarin to NEBIVOPEN 15 or NEBIVOPEN 20:

Warfarin treatment should be stopped and NEBIVOPEN 15 or NEBIVOPEN 20 therapy should be initiated when the INR is < 3,0.

When converting patients from warfarin to NEBIVOPEN, INR values will 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).

SPAF - Converting from NEBIVOPEN to warfarin:

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

In patients converting from NEBIVOPEN 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 NEBIVOPEN and warfarin 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 24 hours after the last dose (see sections 4.5 and 5.2).

SPAF - Converting from parenteral anticoagulants to NEBIVOPEN:

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

Discontinue NEBIVOPEN and give the first dose of parenteral anticoagulant at the time that the NEBIVOPEN dose would have been taken.

SPAF – Elderly population

No dose adjustment is required.

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 section 5.2).

DVT and PE - Posology

Deep venous thrombosis (DVT) and PE treatment:

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

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

It is essential to adhere to the dosage schedule provided. If a dose is missed during the NEBIVOPEN 15, twice daily treatment phase the patient should take NEBIVOPEN 15 immediately to ensure intake of 30 mg per day. In this case, two NEBIVOPEN 15 may be taken at once. The patient should continue with the regular one NEBIVOPEN 15 twice-daily intake as recommended on the following day.

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

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 – Special populations

DVT and PE treatment - patients with hepatic impairment:

NEBIVOPEN 15 and NEBIVOPEN 20 are contraindicated in patients with hepatic disease with or without coagulopathy (see section 4.3).

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

DVT and PE treatment - patients with renal impairment:

No dose adjustment is required if NEBIVOPEN 15 or NEBIVOPEN 20 is administered in patients with mild (creatinine clearance < 80 to 50 ml/min) or moderate (creatinine clearance < 50 to 30 ml/min) renal impairment (see section 5.2).

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, NEBIVOPEN should be used with caution in these patients.

Use of NEBIVOPEN 15 and NEBIVOPEN 20 are not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

DVT and PE treatment - converting from warfarin to NEBIVOPEN 15:

Warfarin treatment should be stopped and NEBIVOPEN 15 therapy should be initiated once the INR is < 2,5.

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

DVT and PE treatment - converting from NEBIVOPEN to warfarin:

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

In patients converting from NEBIVOPEN 15 or NEBIVOPEN 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 NEBIVOPEN and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of NEBIVOPEN 15 or

NEBIVOPEN 20). Once NEBIVOPEN 15 or NEBIVOPEN 20 is discontinued, INR testing may be done reliably 24 hours after the last dose (see sections 4.5 and 5.2).

DVT and PE treatment - converting from parenteral anticoagulants to NEBIVOPEN 15:

For patients currently receiving a parenteral anticoagulant, start NEBIVOPEN 15 at 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 NEBIVOPEN 15 or NEBIVOPEN 20 to parenteral anticoagulants:

Discontinue NEBIVOPEN 15 or NEBIVOPEN 20 and give the first dose of parenteral anticoagulant at the time that the next NEBIVOPEN 15 or NEBIVOPEN 20 dose would have been taken.

DVT and PE treatment – Elderly population

No dose adjustment is required.

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 section 5.2).

Method of administration

NEBIVOPEN is for oral use.

The tablets are to be taken with food.

4.3 Contraindications

- Hypersensitivity to rivaroxaban or any excipient of NEBIVOPEN.
- 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).
- Known existing inherited bleeding disorders
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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

Haemorrhagic risk

NEBIVOPEN should not be used in patients with clinically significant bleeding or with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 4.3).

NEBIVOPEN is not recommended 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
- intraspinal or intracerebral haemorrhage
- intraspinal or intracerebral vascular abnormalities
- shortly after brain, spinal or ophthalmological surgery
- bronchiectasis or history of pulmonary bleeding.

Patients taking NEBIVOPEN have to be carefully observed for signs of bleeding.

NEBIVOPEN administration should be discontinued if severe haemorrhage occurs.

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.

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).

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

Although treatment with NEBIVOPEN 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).

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 5.1 and 5.2).

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

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

Interaction with other medicines

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 (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 should 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 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).

Patients with prosthetic valves

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.

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

Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/TIA.

Haemodynamically unstable 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 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***.*** However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

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

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

Dosing recommendations before and after invasive procedures and surgical intervention:

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 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 contains lactose monohydrate (see section 2). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption, should not take NEBIVOPEN.

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

CYP3A4 and P-gp inhibitors

Co-administration of NEBIVOPEN 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 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), 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 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.

Anticoagulants

Combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) has an additive effect on anti-factor Xa activity, without any additional effects on clotting tests (PT, aPTT). Enoxaparin does 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).

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.

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 but a relevant increase in bleeding time is 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 acetylsalicylic acid) and platelet aggregation inhibitors because these medicines typically increase the bleeding risk (see section 4.4).

SSRIs/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, or from NEBIVOPEN 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 were 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.

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 is observed between warfarin and rivaroxaban as in NEBIVOPEN.

CYP3A4 inducers

Co-administration of NEBIVOPEN with the strong CYP3A4 inducer rifampicin leads 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 co-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.

Co-administration of the H2 receptor antagonist ranitidine and antacid aluminium hydroxide/magnesium hydroxide did not affect rivarobaxan bioavailability and pharmacokinetics.

When NEBIVOPEN 20 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. NEBIVOPEN 15 and 20 are to be taken with food (see sections 4.2 and 5.2).

Laboratory parameters

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

NEBIVOPEN is contraindicated in pregnancy (see section 4.3).

In rats and rabbits, rivaroxaban, as in NEBIVOPEN, 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. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta.

Breastfeeding

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

In rats, rivaroxaban is secreted into breast milk. Therefore, NEBIVOPEN may only be administered after breastfeeding is discontinued.

4.7 Effects on ability to drive and use machines

Adverse reactions like syncope and dizziness have been reported with the use of NEBIVOPEN (see section 4.8 Undesirable effects). 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: Thrombocytosis (incl. increased platelet count), thrombocytopenia

Immune system disorders

Less frequent: Allergic reaction, allergic dermatitis, *a*ngioedema, 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 (including 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, diarrhoea, vomiting

Less frequent: Dry mouth

Hepato-biliary disorders

Frequent: Increase in transaminases

Less frequent: Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase, increased GGT, jaundice, bilirubin conjugated increased (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

Less frequent: Haemarthrosis, muscle haemorrhage

Frequency unknown: Compartment syndrome secondary to a bleeding

Renal and urinary disorders

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

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

nvestigations

Less frequent: Increased LDH, increased lipase, increased amylase,

Injury, poisoning and procedural complications

Frequent: Postprocedural haemorrhage (including post-operative anaemia, and wound haemorrhage), contusion, wound secretion

Less frequent: Vascular pseudoaneurysm

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. 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 as in NEBIVOPEN is not available.

The use of activated charcoal to reduce absorption in case of rivaroxaban as in NEBIVOPEN overdose may be considered. Due to the high plasma protein binding rivaroxaban as in NEBIVOPEN is not expected to be dialysable.

Management of bleeding

Should a bleeding complication arise in a patient receiving NEBIVOPEN, 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 substance should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is very limited clinical experience with the use of these products in individuals receiving NEBIVOPEN.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Class of medicine: 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 (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 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 dependent Inhibition of factor Xa 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 receiving rivaroxaban for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin®), 2 to 4 hours after tablet intake (i.e. at the time of maximum effect), ranged from 17 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 to 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 activated partial thromboplastin time (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.

5.2 Pharmacokinetic properties

Absorption

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

The oral bioavailability for the 20 mg tablet dose is 66 %, under fasting conditions. 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 should be taken with food (see section 4.2).

Under fed conditions rivaroxaban 15 mg and 20 mg tablets demonstrate 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 (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

Of the administered rivaroxaban dose, approximately ⅔ undergoes metabolic degradation, with half then eliminated renally and the other half by the faecal route. The other ⅓ 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 CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. 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 (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 %) (see section 4.2).

Children (up to 18 years of age)

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

Hepatic impairment

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

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) 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, due to significantly impaired medicine clearance which indicates significant liver disease. Unbound AUC is increased 2,6-fold. There are no data in patients with severe hepatic impairment.

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. Patients with moderate hepatic impairment are more sensitive to rivaroxaban, resulting in a steeper PK/PD relationship between concentration and PT.

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

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 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, 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.

There are no data in patients with creatinine clearance < 15 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) (see sections 4.2 and 4.4).

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NEBIVOPEN 15: Hypromellose, microcrystalline cellulose, sodium lauryl sulphate, lactose monohydrate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide (E171), macrogol, iron oxide red (E172).

NEBIVOPEN 20: 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

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands drive

Woodmead

2191

8. REGISTRATION NUMBERS

NEBIVOPEN 15: 53/8.2/0624

NEBIVOPEN 20: 53/8.2/0625

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 June 2022

10. DATE OF REVISION OF THE TEXT

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