## SCHEDULING STATUS

S4

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

**A. Premature discontinuation of MYOROXA increase the risk of thrombotic events:**

**Premature discontinuation of any oral anticoagulant, including MYOROXA, increases the risk of thrombotic events. If anticoagulation with MYOROXA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant (see sections 4.2 and 4.4.).**

**B. Spinal/epidural haematoma:**

**Epidural or spinal hematomas have occurred in patients treated with MYOROXA 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 MYOROXA and neuraxial procedures is not known (see sections 4.4 and 4.8).**

**Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary (see section 4.4). Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see section 4.4).**

## 1 NAME OF THE MEDICINE

MYOROXA 10 film-coated tablets

MYOROXA 15 film-coated tablets

MYOROXA 20 film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated contains 10 mg, 15 mg, or 20 mg rivaroxaban.

*Excipient(s) with known effect:*

MYOROXA 10: Each film-coated tablet contains 28,09 mg lactose monohydrate, see section 4.4.

MYOROXA 15: Each film-coated tablet contains 28,068 mg lactose monohydrate, see section 4.4.

MYOROXA 20: Each film-coated tablet contains 28,09 mg lactose monohydrate, see section 4.4.

MYOROXA contains sugar (lactose monohydrate).

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablets.

MYOROXA 10: Light-red, round shaped, biconvex, film-coated tablets, debossed with "CS" on one side and plain on other side.

MYOROXA 15: Red, round shaped, biconvex, film-coated tablets, debossed with "C4" on one side and plain on other side.

MYOROXA 20: Brown-red, round shaped, biconvex, film-coated tablets, debossed with "C3" on one side and plain on other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

MYOROXA 10 is indicated for:

- Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

MYOROXA 15 and MYOROXA 20 are indicated for:

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

### 4.2 Posology and method of administration

**Posology**

**Prevention of VTE in patients undergoing major orthopaedic surgery of the lower limbs**

The recommended dose is one MYOROXA 10 tablet (10 mg rivaroxaban) taken orally 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 MYOROXA 10 immediately and then continue the following day with once daily intake as before.

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

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

**Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF)**

The recommended dose is one MYOROXA 20 tablet (20 mg rivaroxaban) once daily, which is also the recommended maximum dose.

For patients with moderate renal impairment (creatinine clearance 30 to < 50 ml/min) the recommended dose is one MYOROXA 15 tablet (15 mg rivaroxaban) 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 MYOROXA 20 or MYOROXA 15 immediately and continue with the once daily intake as recommended on the following day. The dose should not be doubled to make up for a missed dose within the same day.

*SPAF – Converting from warfarin to MYOROXA 15 or MYOROXA 20*

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

When converting patients from warfarin to MYOROXA 15 or MYOROXA 20, INR values will be falsely elevated after the intake of MYOROXA 15 or MYOROXA 20. The INR is not valid to measure the anticoagulant activity of MYOROXA 15 or MYOROXA 20, and therefore should not be used (see section 4.5).

*SPAF – Converting from MYOROXA 15 or MYOROXA 20 to warfarin*

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

In patients converting from MYOROXA 15 or MYOROXA 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 MYOROXA 15 or MYOROXA 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of MYOROXA 15 or MYOROXA 20). Once MYOROXA 15 or MYOROXA 20 is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

*SPAF – Converting from parenteral anticoagulants to MYOROXA 15 or MYOROXA 20*

For patients currently receiving a parenteral anticoagulant, start MYOROXA 20 or MYOROXA 15, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g., low molecular weight heparins) or at the time of discontinuation of a continuously administered parenteral medicine (e.g., intravenous unfractionated heparin).

*SPAF – Converting from MYOROXA 15 or MYOROXA 20 to parenteral anticoagulants*

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

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

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

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.

It is essential to adhere to the dosage schedule provided.

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

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

*DVT and PE – Converting from warfarin to MYOROXA 15*

Warfarin treatment should be stopped and MYOROXA 15 therapy should be initiated when the INR is ≤ 2,5.

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

*DVT and PE – Converting from MYOROXA 15 or MYOROXA 20 to warfarin*

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

In patients converting from MYOROXA 15 or MYOROXA 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 MYOROXA 15 or MYOROXA 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of MYOROXA 15 or MYOROXA 20). Once MYOROXA 15 or MYOROXA 20 is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

*DVT and PE – Converting from parenteral anticoagulants to MYOROXA 15*

For patients currently receiving a parenteral anticoagulant, start MYOROXA 15, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g., low molecular weight heparins) or at the time of discontinuation of a continuously administered parenteral medicine (e.g., intravenous unfractionated heparin).

*DVT and PE – Converting from MYOROXA 15 or MYOROXA 20 to parenteral anticoagulants*

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

**Special populations**

There is no need for monitoring of coagulation parameters during treatment with MYOROXA (see section 5.1).

**Hepatic impairment**

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

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see sections 4.3 and 5.2).

**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. Therefore, MYOROXA must be used with caution in these patients. Use of MYOROXA is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

In patients with mild and moderate renal impairment the following dose recommendations apply:

- For the prevention of VTE in patients undergoing major orthopaedic surgery of the lower limbs, no dose adjustment is necessary if MYOROXA 10 is administered in patients with mild (creatinine clearance 50-80 ml/min) or moderate (creatinine clearance 30-49 ml/min) renal impairment (see section 5.2).

- For SPAF, no dose adjustment is necessary if MYOROXA 20 is administered in patients with mild (creatinine clearance 50-80 ml/min) renal impairment. For patients with moderate (creatinine clearance 30-49 ml/min) renal impairment the recommended dose is MYOROXA 15 once daily (see section 5.2).
- For DVT and PE, no dose adjustment is required if MYOROXA 15 or MYOROXA 20 is administered in patients with mild (creatinine clearance 50-80 ml/min) or moderate (creatinine clearance 30-49 ml/min) renal impairment (see section 5.2).

**Elderly (above 65 years), Gender and Body Weight**

No dose adjustment is required for these patient populations.

**Ethnic differences**

No dose adjustment is required based on ethnic differences.

**Paediatric population**

The safety and efficacy of MYOROXA in children aged 0 to 18 years have not been established. No data are available.

**Method of administration**

Oral use.

MYOROXA 10 tablets can be taken with or without food (see section 5.2).

MYOROXA 15 and MYOROXA 20 tablets should be taken **with food** (see section 5.2).

For patients who are unable to swallow whole tablets, MYOROXA tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed MYOROXA 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food. The crushed MYOROXA 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. After the administration of crushed MYOROXA 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding (see section 5.2).

## 4.3 Contraindications

- Hypersensitivity to rivaroxaban or to any of the excipients listed in section 6.1.
- Clinically significant active bleeding (e.g., intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- Persistent triple positive antiphospholipid syndrome (APS).
- Hepatic disease with or without coagulopathy, and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

- 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).
- Safety and efficacy of MYOROXA have not been established in pregnant women or breastfeeding mothers. MYOROXA is therefore contraindicated in pregnancy and breastfeeding (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**

As with other concomitant anticoagulants, patients taking MYOROXA are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. MYOROXA administration should be discontinued if severe haemorrhage occurs (see sections 4.3 and 4.9).

Mucosal bleedings (i.e., epistaxis, gingival, gastrointestinal, genito-urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were reported more frequently during long term MYOROXA treatment compared with vitamin K antagonist treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving MYOROXA 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.

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

Although treatment with MYOROXA 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 sections 5.1 and 5.2).

**Other haemorrhagic risk factors**

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

- acquired bleeding disorders
- uncontrolled severe arterial hypertension
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding.

**DVT and PE treatment - Renal impairment**

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

**SPAF, DVT and PE treatment - 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. Due to the underlying disease these patients are at an increased risk of both bleeding and thrombosis.

Due to limited clinical data MYOROXA should be used with caution in patients with creatinine clearance < 30 to 15 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).

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

**Concomitant medication**

The use of MYOROXA 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 medicines 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).

The azole anti-mycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered (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), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

**Patients with prosthetic valves**

MYOROXA should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of MYOROXA have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that MYOROXA provides adequate anticoagulation in this patient population. Treatment with MYOROXA is not recommended for these patients.

**Patients with antiphospholipid syndrome (APS)**

Direct acting Oral Anticoagulants (DOACs) including MYOROXA 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 warfarin; a vitamin K antagonist therapy (see section 4.3).

**Hip fracture surgery**

The use of MYOROXA to prevent VTE has not been studied in patients undergoing hip fracture surgery to evaluate efficacy and safety.

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

Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited. No data are available for such patients with a history of stroke/transient ischaemic attack (TIA).

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

MYOROXA 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 MYOROXA have not been established in these clinical situations.

**Neuraxial (spinal/epidural) anaesthesia or puncture**

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary.

Prior to neuraxial intervention the doctor 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 MYOROXA 15 or MYOROXA 20 in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of MYOROXA 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 and should be weighed against the urgency of a diagnostic procedure.

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 adult patients and 26 hours in elderly patients should elapse after the last administration of MYOROXA (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next MYOROXA dose is administered.

If traumatic puncture occurs the administration of MYOROXA should be delayed for 24 hours.

**Surgery and interventions**

If an invasive procedure or surgical intervention other than elective hip or knee replacement surgery is required, MYOROXA 10 should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the doctor.

If an invasive procedure or surgical intervention is required, MYOROXA 15 or MYOROXA 20 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.

MYOROXA 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 MYOROXA (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. MYOROXA 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.

**QTc prolongation**

No QTc prolonging effect was observed with MYOROXA.

**Information about excipients**

MYOROXA tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MYOROXA.

MYOROXA contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free.

**4.5 Interaction with other medicines and other forms of interaction**

**Pharmacokinetic interactions:**

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

*CYP inhibition:*

Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.

*CYP induction:*

Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

*Effects on MYOROXA:*

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

Co-administration of MYOROXA with the azole-antimycotic ketoconazole (400 mg once a day) a strong CYP 3A4 and P-gp inhibitor, led to a 2,6 fold increase in mean rivaroxaban AUC and a 1,7 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk (see section 4.4).

Co-administration of MYOROXA with the HIV protease inhibitor ritonavir (600 mg twice daily), a strong CYP 3A4 and P-gp inhibitor, led to a 2,5 fold increase in mean rivaroxaban AUC and a 1,6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk (see section 4.4). Data on the co-administration of MYOROXA with the HIV protease inhibitor ritonavir (100 mg twice daily) is not available.

Therefore, the use of MYOROXA is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These medicines are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Medicines 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, led to a 1,5 fold increase in mean rivaroxaban AUC and a 1,4 fold increase in $C_{max}$. The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times a day), which inhibits CYP3A4 and P-gp moderately, led to a 1,3 fold increase in mean rivaroxaban AUC and $C_{max}$. The interaction with erythromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. In subjects with mild renal impairment erythromycin (500 mg three times a day) led to a 1,8 fold increase in mean rivaroxaban AUC and 1,6 fold increase in $C_{max}$ when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2,0 fold increase in mean rivaroxaban AUC and 1,6 fold increase in $C_{max}$ when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1,4 fold increase in mean rivaroxaban AUC and a 1,3 fold increase in mean $C_{max}$. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

**Pharmacodynamic interactions:**

**Anticoagulants**

After combined administration of enoxaparin (40 mg single dose) with MYOROXA (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 section 4.4).

**NSAIDs/platelet aggregation inhibitors**

No clinically relevant prolongation of bleeding time was observed after concomitant administration of MYOROXA (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 MYOROXA was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with MYOROXA (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

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

**SSRIs/SNRIs**

As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used with MYOROXA, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups during clinical studies.

**Warfarin**

Converting patients from the vitamin K antagonist warfarin (INR 2,0 to 3,0) to MYOROXA 20 or from MYOROXA 20 to warfarin (INR 2,0 to 3,0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of MYOROXA during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of MYOROXA.

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 MYOROXA) as this test is minimally affected by rivaroxaban at this time point. No pharmacokinetic interaction was observed between warfarin and MYOROXA.

**CYP3A4 inducers**

Co-administration of MYOROXA 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 MYOROXA with other strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, or St. John's Wort (Hypericum perforatum)) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

**Other concomitant therapies**

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

**Laboratory parameters**

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

**4.6 Fertility, pregnancy and lactation**

**Women of child-bearing potential**

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

**Pregnancy**

Safety and efficacy of MYOROXA have not been established in pregnant women. Due to the potential reproductive toxicity in animals, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, MYOROXA is contraindicated during pregnancy (see section 4.3).

**Breastfeeding**

Safety and efficacy of MYOROXA have not been established in breastfeeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, MYOROXA may only be administered after breastfeeding is discontinued (see section 4.3).

**Fertility**

No specific studies with MYOROXA in humans have been conducted to evaluate effects on fertility.

**4.7 Effects on ability to drive and use machines**

MYOROXA has minor influence on the ability to drive and use machines. Adverse reactions like syncope and dizziness have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

**4.8 Undesirable effects**

| System organ class (MedDRA) | Frequent | Less frequent | Not known |
|---|---|---|---|
| **Blood and lymphatic system disorders** | Anaemia (incl. respective laboratory parameters) | Thrombocytosis (incl. platelet count increased) [A], thrombocytopenia | |
| **Immune system disorders** | | Allergic reaction, dermatitis allergic, angioedema and allergic oedema, anaphylactic reactions including anaphylactic shock | |
| **Nervous system** | Dizziness, headache | Cerebral and intracranial | |

| System organ class (MedDRA) | Frequent | Less frequent | Not known |
|---|---|---|---|
| **disorders** | | haemorrhage, syncope | |
| **Eye disorders** | Eye haemorrhage (incl. conjunctival haemorrhage) | | |
| **Cardiac disorders** | | Tachycardia | |
| **Vascular disorders** | Hypotension, haematoma | | |
| **Respiratory, thoracic, and mediastinal disorders** | Epistaxis, haemoptysis | | |
| **Gastrointestinal disorders** | Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation [A], diarrhoea, vomiting [A] | Dry mouth | |
| **Hepato-biliary disorders** | Increase in transaminases | 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 (incl. hepatocellular injury) | |
| **Skin and subcutaneous tissue disorders** | Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage | Urticaria, Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis, DRESS syndrome | |
| **Musculoskeletal and connective tissue disorders** | Pain in extremity [A] | Haemarthrosis, muscle haemorrhage | Compartment syndrome secondary to a bleeding |
| **Renal and urinary disorders** | Urogenital tract haemorrhage (incl. haematuria and menorrhagia [B]), renal impairment (incl. blood creatinine increased, blood urea increased) | | Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion |
| **General disorders and administration site conditions** | Fever [A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia) | Feeling unwell (incl. malaise), localised oedema [A] | |

| System organ class (MedDRA) | Frequent | Less frequent | Not known |
|---|---|---|---|
| **Investigations** | | Increased LDH [A], increased lipase [A], increased amylase [A] | |
| **Injury, poisoning and procedural complications** | Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion, wound secretion [A] | 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**

Due to the pharmacological mode of action, the use of MYOROXA may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. 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”). Mucosal bleedings (i.e., epistaxis, gingival, gastrointestinal, genito-urinary including abnormal vaginal or increased menstrual bleeding) and anaemia have been reported more frequently during long term RALAN treatment compared with vitamin K antagonist treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups, e.g., those patients with uncontrolled severe arterial hypertension, impaired renal and hepatic function and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged.

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 MYOROXA. 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 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**

Rare 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 reversal medicine antagonising the pharmacodynamic effect of MYOROXA is not available. The use of activated charcoal to reduce absorption in case of MYOROXA 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 MYOROXA, the next administration 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, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicines in individuals receiving MYOROXA. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

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

## 5 PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

A 8.2 Anticoagulants

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

**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.

**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 is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e., at the time of maximum effect) ranged from 13 to 25 s (baseline values before surgery 12 to 15 s).

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e., at the time of maximum effect) for 15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8-16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18-30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1-4 hours after tablet intake (i.e., at the time of maximum effect) in patients treated with 20 mg once daily ranged from 14 to 40 s and in patients with moderate renal impairment treated with 15 mg once daily from 10 to 50 s. At trough (16-36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3-factor 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 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.

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 rapidly absorbed with maximum concentrations (Cmax) appearing 2-4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80-100 %) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or Cmax at the 10 mg dose. MYOROXA 10 mg tablets can be taken with or without food.

Due to a reduced extent of absorption an oral bioavailability of 66 % was determined for the 20 mg tablet 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. MYOROXA 15 mg and 20 mg are to be taken with food (see section 4.2).

Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily in fasting state. Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. 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 %, apart from on the day of surgery and the following day when variability in exposure is high (70 %).

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29 % and 56 % decrease in AUC and Cmax compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure.

**Distribution**

Plasma protein binding in adults 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**

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

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance substance. After intravenous administration of a 1 mg dose the elimination half-life is about 4,5 hours. After oral administration, the elimination becomes absorption rate limited. 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 (see section 4.2).

*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).

*Inter-ethnic differences*

No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese, or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics (see section 4.2).

*Hepatic impairment*

The effect of hepatic impairment on rivaroxaban pharmacokinetics has been studied in subjects categorised according to the Child Pugh classification, a standard procedure in clinical development. In patients for whom anticoagulation is intended, the critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver. Since this aspect is captured by only one of the five clinical/biochemical measurements composing the Child Pugh classification system, the bleeding risk in patients may not clearly correlate with this classification scheme.

Rivaroxaban is contraindicated in patients with hepatic disease with or without coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1,2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2,3 fold compared to healthy volunteers. Unbound AUC was increased 2,6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment (classified as Child Pugh C) (see sections 4.2 and 4.3).

The inhibition of factor Xa activity was increased by a factor of 2,6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2,1. The global clotting test PT assesses the extrinsic pathway that comprises of the coagulation factors VII, X, V, II, I which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

*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 volunteers (see sections 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate, and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1,5, 1,9 and 2,0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1,3, 2,2 and 2,4 respectively.

There are no data in patients with creatinine clearance < 15 ml/min.

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 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.

*Concomitant administration of strong CYP 3A4 inducers*

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

In a Phase IIb trial, the PK/PD of an adapted rivaroxaban dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP 3A4 and P-gp inducer (rifampicin or phenytoin). The adapted dosing regimen in these patients led to a similar exposure and pharmacodynamics when compared to patients treated for DVT (15 mg twice daily in the first 3 weeks of treatment, followed by 20 mg once daily) without the concomitant administration of a strong CYP 3A4 inducer.

**Pharmacokinetic data in patients**

In patients receiving rivaroxaban for prevention of VTE, 10 mg once daily, the geometric mean concentration (90 % prediction interval) 2-4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 101 (7-273) and 14 (4-51) µg/l, respectively.

In patients receiving rivaroxaban for treatment of acute DVT, 20 mg once daily, the geometric mean concentration (90 % prediction interval) 2-4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22-535) and 32 (6-239) µg/l, respectively.

**Pharmacokinetic/pharmacodynamic relationship**

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5-30 mg twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an $E_{max}$ model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

In patients undergoing major orthopaedic surgery, baseline factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

**Paediatric population**

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Microcrystalline cellulose

Lactose monohydrate

Croscarmellose sodium

Hypromellose

Sodium lauryl sulfate

Colloidal anhydrous silica

Magnesium stearate

*Film-coating – 10 mg tablets:*

Opadry Pink (04F540031) consisting of:

- Hypromellose (E464)
- Iron oxide red (E172)
- Titanium dioxide (E171)
- Macrogol (E1521)

*Film-coating – 15 mg tablets:*

Opadry Brown (04F565029) consisting of

- Hypromellose (E464)
- Iron oxide red (E172)
- Titanium dioxide (E171)
- Macrogol (E1521)

*Film-coating – 20 mg tablets:*

Opadry Brown (04F565025) consisting of:

- Hypromellose (E464)
- Iron oxide red (E172)
- Titanium dioxide (E171)
- Macrogol (E1521)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original packaging until required for use.

**6.5 Nature and contents of container**

Transparent Aluminium//PVC/PVDC foil blisters in cartons.

MYOROXA 10 pack sizes: 5, 10, 30 or 100 film-coated tablets.

MYOROXA 15 pack sizes: 10, 14, 28, 42, 98 or 100 film-coated tablets.

MYOROXA 20 pack sizes: 10, 14, 28, 98 or 100 film-coated tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

## 8 REGISTRATION NUMBER

MYOROXA 10: 56/8.2/0551

MYOROXA 15: 56/8.2/0552

MYOROXA 20: 56/8.2/0553

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 October 2023

## 10 DATE OF REVISION OF THE TEXT

18 August 2023