**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product:

Zeroban 10 mg film-coated tablets

## 2. Qualitative and quantitative composition

Each film-coated tablet contains 10 mg rivaroxaban.

Excipient with known effect:

Each film-coated tablet contains 81.0 mg lactose, see section 4.4. For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film-coated tablet.

A brown coloured round shaped, biconvex, film coated tablet plain on both side.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Rivaroxaban is a prescription medicine used to reduce the risk of stroke and blood clots in people with atrial fibrillation, not caused by a heart valve problem.

Rivaroxaban is also used to treat deep vein thrombosis and pulmonary embolism, and to help reduce the risk of these conditions occurring again, and to reduce the risk of forming a blood clot in the legs and lungs of people who have just had knee or hip replacement surgery.

### 4.2 Posology and method of administration

Prevention of stroke and systemic embolism in adults

The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

Therapy with Zeroban should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding

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

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

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

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

transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.
When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Zeroban 10 mg once daily, a dose of Zeroban 20 mg once daily should be considered.
The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

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

To support the dose switch from 15 mg to 20 mg after Day 21 a first 4 weeks treatment initiation pack of Zeroban for treatment of DVT/PE is available.
If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take Zeroban immediately to ensure intake of 30 mg Zeroban per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase, the patient should take Zeroban immediately, and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.
Treatment of VTE and prevention of VTE recurrence in children and adolescents
Zeroban treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment.
The dose for children and adolescent is calculated based on body weight.
- Body weight of 50 kg or more:
a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
Converting from Vitamin K Antagonists (VKA) to Zeroban - Prevention of stroke and systemic embolism:

VKA treatment should be stopped and Zeroban therapy should be initiated when the International Normalised Ratio (INR) is ≤ 3.0.
- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:

VKA treatment should be stopped and Zeroban therapy should be initiated once the INR is ≤ 2.5.
When converting patients from VKAs to Zeroban, INR values will be falsely elevated after the intake of Zeroban. The INR is not valid to measure the anticoagulant activity of Zeroban, and therefore should not be used.
Converting from Zeroban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Zeroban to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Zeroban can contribute to an elevated INR.
In patients converting from Zeroban to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both Zeroban and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Zeroban. Once Zeroban is discontinued INR testing may be done reliably at least 24 hours after the last dose.
Paediatric patients:
Children who convert from Zeroban to VKA need to continue Zeroban for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Zeroban. Co-administration of Zeroban and VKA is advised to continue until the INR is ≥ 2.0. Once Zeroban is discontinued INR testing may be done reliably 24 hours after the last dose.
Converting from parenteral anticoagulants to Zeroban
For adult and paediatric patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Zeroban 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).
Converting from Zeroban to parenteral anticoagulants
Discontinue Zeroban and give the first dose of parenteral anticoagulant at the time the next Zeroban dose would be taken.

<u>Paediatric population</u>
The safety and efficacy of Zeroban in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

Method of administration: For oral use.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active clinically significant bleeding.

Lesion or condition, if considered to be a significant risk for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

Concomitant treatment with any other anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

Concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (see section 4.4).

Concomitant treatment of CAD/PAD with ASA in patients with previous haemorrhagic or lacunar stroke, or any stroke within a month (see section 4.4).

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).

Pregnancy and breast-feeding (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 anticoagulants, patients taking Zeroban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Zeroban

administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. Therefore, the use of rivaroxaban in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after 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 rivaroxaban does not require routine monitoring of exposure, rivaroxaban levels measured with a calibrated quantitative anti-factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery (see sections 5.1 and 5.2).

*Paediatric population*
There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection (see section 5.1). The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment

In adult 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. Rivaroxaban tablet is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2).
Zeroban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5).

Zeroban is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 $m^2$), as no clinical data is available.

Interaction with other medicinal products

The use of Zeroban 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 is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (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 sections 4.5).

Other haemorrhagic risk factors

As with other antithrombotics, rivaroxaban is not recommended in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

Patients with cancer
Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumour location, antineoplastic therapy and stage of disease. Tumours located in the gastrointestinal or genitourinary tract have been associated with an increased risk of bleeding during rivaroxaban therapy.
In patients with malignant neoplasms at high risk of bleeding, the use of rivaroxaban is contraindicated.

Patients with prosthetic valves

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

patients with prosthetic heart valves; therefore, there are no data to support that rivaroxaban provides adequate anticoagulation in this patient population. Treatment with rivaroxaban 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

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 (see sections 4.2 and 5.1). 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

Rivaroxaban 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 rivaroxaban 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 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 postoperative use of indwelling epidural catheters or the concomitant use of medicinal products 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 physician should consider the potential benefit versus

the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 20 mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban 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 rivaroxaban (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

No data is available on the timing of the placement or removal of neuraxial catheter in children while on rivaroxaban. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, rivaroxaban 20 mg should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician.

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

Rivaroxaban 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 physician (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 in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. Rivaroxaban 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

Rivaroxaban tablet contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product also contains less than 23 mg sodium per dosage unit, that is to say essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section 4.4 should be taken into account for the paediatric population.

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban $C_{max}$, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg twice a day), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, 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 Cmax. 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 $CR_{max}$ 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 $CR_{max}$ 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.

Anticoagulants

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

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

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed 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 medicinal products 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 in the rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, 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 rivaroxaban.

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

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban 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 rivaroxaban 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 rivaroxaban 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 rivaroxaban (see section 5.1)

## 4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety and efficacy of Zeroban have not been established in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated during pregnancy (see section 4.3).

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Breast-feeding

Safety and efficacy of Zeroban have not been established in breast-feeding women. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, Zeroban is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy.

Fertility

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

## 4.7 Effects on ability to drive and use machines.

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

## 4.8 Undesirable effects

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions to the pharmacy and poisons board, through the Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen phase III studies in adults including 53,103 patients exposed to rivaroxaban, and in two phase II and one phase III paediatric studies including 412 patients. See phase III studies as listed in table 1.

Table 1: Number of patients studied, total daily dose and maximum treatment duration in adult and paediatric phase III studies

| **Indication** | **Number of patients*** | **Total daily dose** | **Maximum treatment duration** |
|---|---|---|---|
| Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery | 6,097 | 10 mg | 39 days |
| Prevention of VTE in medically ill patients | 3,997 | 10 mg | 39 days |
| Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrence | 6,790 | Day 1 - 21: 30 mg<br>Day 22 and onwards: 20 mg<br>After at least 6 months: 10 mg or 20 mg | 21 months |
| Treatment of VTE and prevention of | 329 | Body weight-adjusted | 12 months |
| VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment | | dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily | |

| | | | |
|---|---|---|---|
| Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation | 7,750 | 20 mg | 41 months |
| Prevention of atherothrombotic events in patients after an ACS | 10,225 | 5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine | 31 months |
| Prevention of atherothrombotic events in patients with CAD/PAD | 18,244 | 5 mg co-administered with ASA or 10 mg alone | 47 months |
| * Patients exposed to at least one dose of rivaroxaban | | | |

The most commonly reported adverse reactions in patients receiving rivaroxaban were bleedings (see section 4.4. and 'Description of selected adverse reactions' below) (Table 2). The most commonly reported bleedings were epistaxis (4.5 %) and gastrointestinal tract haemorrhage (3.8 %).

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

| **Indication** | **Any bleeding** | **Anaemia** |
|---|---|---|
| Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery | 6.8% of patients | 5.9% of patients |
| Prevention of VTE in medically ill patients | 12.6% of patients | 2.1% of patients |
| Treatment of DVT, PE and prevention of recurrence | 23% of patients | 1.6% of patients |
| Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment | 39.5% of patients | 4.6% of patients |
| Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation | 28 per 100 patient years | 2.5 per 100 patient years |
| Prevention of atherothrombotic events in patients after an ACS | 22 per 100 patient years | 1.4 per 100 patient years |
| Prevention of atherothrombotic events in patients with CAD/PAD | 6.7 per 100 patient years | 0.15 per 100 patient years** |
| * For all rivaroxaban studies all bleeding events are collected, reported and adjudicated. ** In the COMPASS study, there is a low anaemia incidence as a selective approach to adverse event collection was applied | | |

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarised in table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
very common (≥1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),
very rare (< 1/10,000)
not known (cannot be estimated from the available data)

Table 3: All adverse reactions reported in adult patients in phase III clinical studies or through post-marketing use* and in two phase II and one phase III studies in paediatric patients

| **Common** | **Uncommon** | **Rare** | **Very rare** | **Not known** |
|---|---|---|---|---|
| **Blood and lymphatic system disorders** | | | | |
| Anaemia (incl. respective laboratory parameters) | Thrombocytosis (incl. platelet count increased) [A], thrombocytopenia | | | |
| **Immune system d isorders** | | | | |
| | Allergic reaction, dermatitis allergic, angioedema and allergic oedema | | Anaphylactic reactions including anaphylactic shock | |
| **Nervous system disorders** | | | | |
| Dizziness, headache | Cerebral and intracranial haemorrhage, syncope | | | |
| **Eye disorders** | | | | |
| Eye haemorrhage (incl. conjunctival haemorrhage) | | | | |
| **C ardiac disorders** | | | | |
| | Tachycardia | | | |
| **Vascular disorders** | | | | |
| Hypotension, haematoma | | | | |

| | | | | |
|---|---|---|---|---|
| **Respiratory, thoracic and mediastina l dis orders** | | | | |
| 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 | | | |
| **Hepatobiliary disorders** | | | | |
| Increase in transaminases | Hepatic impairment, increased bilirubin, increased blood alkaline phosphatase [A], | Jaundice, bilirubin conjugated increased (with or without concomitant increase of ALT), | | |
| | increased GGT [A] | 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 disor ders** | | | | |

| | | | | |
|---|---|---|---|---|
| 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 | | |
| **Investigatio ns** | | | | |
| | Increased LDH[A], increased lipase [A], increased amylase [A] | | | |
| **Injury, poisoning and procedural co mplications** | | | | |
| 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)
* A pre-specified selective approach to adverse event collection was applied. As incidence of adverse reactions did not increase and no new adverse reaction was identified, COMPASS study data were not included for frequency calculation in this table.

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban 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"). In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequently during long term rivaroxaban treatment compared with 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, 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 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 rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

## 4.8 Overdose

In adults, rare cases of overdose up to 1,960 mg have been reported. In case of overdose, the patient should be observed carefully for bleeding complications or other adverse reactions. There is limited data available in children. 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 in adults, however, no data is available at supratherapeutic doses in children.

A specific reversal agent (andexanet alfa) antagonising the pharmacodynamic effect of rivaroxaban is available (refer to the Summary of Product Characteristics of andexanet alfa).

The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban 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, either the administration of a specific factor Xa inhibitor reversal agent (andexanet alfa), which antagonises the pharmacodynamic effect of rivaroxaban, or a specific procoagulant reversal agent, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered. However, there is currently very limited clinical experience with the use of these medicinal products in individuals receiving rivaroxaban. 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 rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

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

### 5.2 Pharmacokinetic properties

Absorption

The following information is based on the data obtained in adults.

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

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or $C_{max}$ at the 2.5 mg and 10 mg dose.

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. Rivaroxaban 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 doseproportionality. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

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

Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in AUC and $C_{max}$ 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.

Bioavailability (AUC and $C_{max}$) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. Given the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

<u>Paediatric population</u>
Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute

bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food.

Rivaroxaban 20 mg tablets should be taken with feeding or with food (see section 4.2).

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 $V_{ss}$ being approximately 50 litres.

Paediatric population
No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. Vss estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

Biotransformation and elimination
In adults, 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.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL

estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition halflives ($t_{1/2}$) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

## 5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and juvenile toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ-specific toxicity was seen

# 6. Pharmaceutical particulars

## 6.1 List of excipients

Microcrystalline cellulose (PH 112)
Betacyclodextrin
Croscarmellose sodium
H.P .M.C. (E-5)
Sodium lauryl suphate
Purified water
Lactose
Crospovidone
Colloidal silicon dioxide
Magnesium stearate
Hydroxypropyl Methyl Cellulose
Poly Ethylene Glycol

Ferric Oxide Red
Titanium Dioxide
Talcum BP

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
3 years

**6.4 Special precautions for storage:**
Do not store above 30℃

**6.5 Nature and contents of container**
10 tablets Alu-Alu blister packed in carton with an insert

**6.6 Special precautions for disposal and other handling:**
No special requirements.

**7. Marketing authorization holder and manufacturing site addresses**

**Marketing authorisation holder**
Avetina Life Sciences Ltd

**Manufacturing site address**
4 CARE LIFESCIENCE PVT. LTD.
Address: Survey no. 23/3P & 24, opp. Jeans factory, Daduramvistar, village- Bagdol. Tal. Kathlal, Dist. Kheda-387630, Gujarat, India.

**8. Marketing authorization number**
CTD9836

**9. Date of first registration**
12/04/2023

**10. Date of revision of the text:**
26/11/2021

**11. Dosimetry:**
Not Applicable

**12. Instructions for Preparation of Radiopharmaceuticals:**
Not Applicable