SUMMARY OF PRODUCT CHARACTERISTICS HARTEZE 20 MG FILM COATED TABLET

1. **Name of the Medicinal Product**

   Harteze 20 mg film coated Tablet

2. **Qualitative and Quantitative Composition**

   Each film coated tablet contains 20 mg of Rivaroxaban.

3. **Pharmaceutical Form**

   Film coated Tablet

4. **Clinical Particulars**

4.1 Therapeutic Indications

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

4.2 Posology and Method of administration

Continued treatment of deep-vein thrombosis, (following initial treatment) Continued treatment of pulmonary embolism, (following initial treatment) Prophylaxis of recurrent deep-vein thrombosis, Prophylaxis of recurrent pulmonary embolism.

BY MOUTH

▸ Adult: 20 mg once daily, to be taken with food

Prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and with at least one of the following risk factors: congestive heart failure, hypertension, previous stroke or transient ischaemic attack, age ≥ 75 years, or diabetes mellitus.

BY MOUTH

▸ Adult: 20 mg once daily, to be taken with food

4.3 Contraindication

Active bleeding in acute coronary syndrome—previous stroke, in acute coronary syndrome—transient ischaemic attack , malignant neoplasms, oesophageal varices, recent brain surgery, recent gastrointestinal ulcer, recent intracranial haemorrhage, recent ophthalmic surgery, recent spine surgery, significant risk of major bleeding, vascular aneurysm.

4.4 Special warnings and precautions for use

Haemorrhagic risk

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. 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 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.

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. Harteze 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. In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase Rivaroxaban plasma concentrations Harteze is to be used with caution.

Interaction with other medicinal products

The use of Harteze 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. 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. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Other haemorrhagic risk factors

As with other antithrombotics, Rivaroxaban is to be used with caution in patients with an increased bleeding risk such as:

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

Hip fracture surgery

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

Information about excipients

Harteze contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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 Harteze is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. 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}. 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}. This increase is not considered clinically relevant.

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 increases in $C_{max}$when compared to subjects with normal renal function. 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}. Given the limited clinical data available with dronedarone, co-administration with Rivaroxaban should be avoided.

<u>Anticoagulants</u>

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.

<u>NSAIDs/platelet aggregation inhibitors</u>

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.

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.

4.6 Pregnancy and lactation

Pregnancy

Safety and efficacy of Harteze have not been established in pregnant women. Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that Rivaroxaban passes the placenta, Harteze is contraindicated during pregnancy.

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

Breast feeding

Safety and efficacy of Harteze have not been established in breast feeding women. Data from animals indicate that Rivaroxaban is secreted into milk. Therefore Harteze is contraindicated during breast feeding. 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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Common or very common: Abdominal pain, constipation, diarrhea, dizziness, dyspepsia, haemorrhage, headache, hypotension, nausea, pain in extremities, pruritus, rash, renal impairment, vomiting

Uncommon: Angioedema, dry mouth, malaise, syncope, tachycardia, thrombocythaemia

Rare: Jaundice, oedema

5 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 antidote antagonising the pharmacodynamic effect of Rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of Rivaroxaban overdose may be considered.

6 Pharmacological Properties

6.1 Pharmacodynamic Properties

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.

6.2 Pharmacokinetic Properties

Absorption

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%) Rivaroxaban pharmacokinetics is approximately linear up to about 15 mg once daily. At higher doses Rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose.

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.

Distribution

Plasma protein binding in humans is high at approximately 92 % to 95 %, with serum albumin being the main binding component.

Biotransformation and elimination

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.

6.3 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.

7 Pharmaceutical Particulars

6.2 list of Excipients

Lactose BP

Microcrystalline cellulose PH 101

Sodium lauryl sulphate BP

Croscarmellose sodium BP (Dried)

Hypromellose 5 cps BP

Magnesium Stearate BP

COATING

Novomix 10008 (Ready mix coating material)

Red iron oxide

Purified water BP

7.2 Incompatibilities

Not Applicable

7.3 Shelf life

3 Years

7.4 Special precautions for storage

Store in a dry place below 30˚C. Protect from light.

Keep all medicines out of the reach of children.

7.5 Nature and contents of container

Alu-Alu pack.

7.6 Instructions for use, handling and disposal

No special requirements.

8 REGISTRANT

Cosmos Limited

9 MANUFACTURER

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