1. **NAME OF DRUG PRODUCT**

Rivaxo (Rivaroxaban) Tablets 20mg

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains:
Rivaroxaban ..... 20mg

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Red colored, round shaped film coated tablet, plain on both sides.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic Indications**

- Reduction of Risk of Stroke and Systemic Embolism in Non-valvular Atrial Fibrillation Rivaxo (Rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

- Treatment of Deep Vein Thrombosis
  Rivaxo (Rivaroxaban) is indicated for the treatment of deep vein thrombosis (DVT).

- Treatment of Pulmonary Embolism
  Rivaxo (Rivaroxaban) is indicated for the treatment of pulmonary embolism (PE).

- Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism
  Rivaxo (Rivaroxaban) is indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and/or PE.

- Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
  Rivaxo (Rivaroxaban) is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

4.2 **Posology and Method of Administration**

Rivaxo (Rivaroxaban) Tablets is administered orally.

| Indication | Dosage | |
|---|---|---|
| Reduction in Risk of Stroke in Non valvular Atrial Fibrillation | CrCl >50 mL/min | 20mg once daily with the evening meal |
| | CrCl 15 to 50 mL/min | 15mg once daily with the evening |
| | | meal |
| Treatment of DVT Treatment of PE | 15mg twice daily with food, for first 21 days | |
| | ▼after 21 days, transition to ▼ | |
| | 20mg once daily with food, for remaining treatment | |
| Reduction in the Risk of Recurrence of DVT and of PE | 20mg once daily with food | |
| Prophylaxis of DVT Following Hip or Knee Replacement Surgery | Hip replacement | 10mg once daily for 35 days |
| | Knee replacement | 10mg once daily for 12 days |

Switching from Warfarin to Rivaxo (Rivaroxaban):
When switching patients from warfarin to Rivaxo (Rivaroxaban), discontinue warfarin and start Rivaxo (Rivaroxaban) as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

The duration of therapy should be individualized after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk Factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk Factors or idiopathic DVT or PE.
If a dose is missed during the 15mg twice daily treatment phase (day 1 - 21), the patient should take Rivaxo (Rivaroxaban) immediately to ensure intake of 30mg Rivaxo (Rivaroxaban) per day. In this case two 15mg tablets may be taken at once. The patient should continue with the regular 15mg twice daily intake as recommended on the following day.
If a dose is missed during the once daily treatment phase (day 22 and onwards), the patient should take Rivaxo (Rivaroxaban) 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.

Converting from Rivaxo (Rivaroxaban) to Vitamin K antagonists (VKA):
There is a potential for inadequate anticoagulation during the transition from Rivaxo (Rivaroxaban) to VKA. Continuous adequate anticoagulation should be

ensured during any transition to an alternate anticoagulant. It should be noted that Rivaxo (Rivaroxaban) can contribute to an elevated INR.
In patients converting from Rivaxo (Rivaroxaban) 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 Rivaxo (Rivaroxaban) and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Rivaxo (Rivaroxaban). Once Rivaxo (Rivaroxaban) is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Converting from parenteral anticoagulants to Rivaxo (Rivaroxaban):
For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start Rivaxo (Rivaroxaban) 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 Rivaxo (Rivaroxaban) to parenteral anticoagulants:
Give the first dose of parenteral anticoagulant at the time the next Rivaxo (Rivaroxaban) dose would be taken.

Patients with renal impairment:
In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15mg once daily.
- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: Patients should be treated with 15mg twice daily for the first 3 weeks.

Thereafter, the recommended dose is 20mg once daily. A reduction of the dose from 20mg once daily to 15mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min).

Patients undergoing cardioversion:
Rivaxo (Rivaroxaban) can be initiated or continued in patients who may require cardioversion. For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Rivaxo (Rivaroxaban) treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation. For all patients, confirmation should be sought prior to cardioversion that the patient has taken Rivaxo (Rivaroxaban) as prescribed.

Pediatric population:
Rivaxo (Rivaroxaban) is not recommended for use in children below 18 years of age.

Discontinuation for surgery and other interventions:
If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, Rivaxo (Rivaroxaban) should be stopped at least 24 hours before the procedure to reduce the risk of bleeding. Rivaxo (Rivaroxaban) should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established, noting that the time to onset of therapeutic effect is short.

**Method of Administration**

For oral use:
For patients who are unable to swallow whole tablets, 10mg, 15mg or 20mg Rivaxo (Rivaroxaban) tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed Rivaxo (Rivaroxaban) 15mg or 20mg tablet, the dose should be immediately followed by food.

Administration via nasogastric (NG) tube or gastric feeding tube:
After confirming gastric placement of the tube, 10mg, 15mg or 20mg Rivaxo (Rivaroxaban) tablets may be crushed and suspended in 50mL of water and administered via an NG tube or gastric feeding tube. Since rivaroxaban absorption is dependent on the site of drug release, avoid administration of Rivaxo (Rivaroxaban) distal to the stomach which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed Rivaxo (Rivaroxaban) 15mg or 20mg tablet, the dose should then be immediately followed by enteral feeding.

## 4.3 Contraindications

Rivaroxaban is contraindicated in patients with:
- Hypersensitivity to rivaroxaban or to any of the excipient of product.
- 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 hemorrhage, 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 or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.
- Pregnancy and breast feeding.

## 4.4 Special warnings and special precautions for use

**Hemorrhagic risk**
As with other anticoagulants, patients taking rivaroxaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of hemorrhage. Rivaroxaban administration should be discontinued if severe hemorrhage occurs.

**Renal impairment**
Rivaroxaban 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. Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

**Other hemorrhagic 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 prosthetic valves**
Treatment with rivaroxaban is not recommended for the patients with prosthetic heart valves.

Hemodynamically 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 hemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

Increased risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant increases the risk of thrombotic events. If anticoagulation with rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

**Spinal/epidural anesthesia or puncture**

When neuraxial anesthesia (spinal/epidural anesthesia) 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 hematoma which can result in long-term or permanent paralysis. 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.

Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is low.

For the removal of an epidural catheter and based on the general PK characteristics at least 2 x half-life, i.e., at least 18 hours in young patients and 26 hours in elderly patients should elapse after the last administration of rivaroxaban. 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.

**Dosing recommendations before and after invasive procedures and surgical intervention**

If an invasive procedure or surgical intervention is required, Rivaroxaban 20mg 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.

**Elderly population**

Increasing age may increase hemorrhagic risk.

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

**CYP3A4 and P-gp inhibitors**

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 (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 (2.6fold on average) which may lead to an increased bleeding risk.

**NSAIDs/platelet aggregation inhibitors**
Care is to be taken if patients are treated concomitantly with medicinal products affecting hemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

**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.

Laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban.

## 4.6 **Pregnancy and Lactation**

Pregnancy
Safety and efficacy of rivaroxaban 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, Rivaroxaban is contraindicated during pregnancy. Women of child bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

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

## 4.7 Undesirable effects

Common
Anemia (incl. respective laboratory parameters), dizziness, headache, eye hemorrhage (incl. conjunctival hemorrhage), hypotension, hematoma, epistaxis, hemoptysis, gingival bleeding, gastrointestinal tract hemorrhage

(incl. rectal hemorrhage), gastrointestinal an abdominal pains, dyspepsia, nausea, constipation, diarrhea, vomiting, pruritus (incl. uncommon cases of generalized pruritus), rash, ecchymosis, cutaneous and subcutaneous hemorrhage, pain in extremity, urogenital tract hemorrhage (incl. hematuria and menorrhagia), renal impairment (incl. blood creatinine increased, blood urea increased), fever, peripheral edema, decreased general strength and energy (incl. fatigue and asthenia), increase in transaminases, post procedural hemorrhage (incl. postoperative anemia, and wound hemorrhage), contusion and wound secretion.

Uncommon
Thrombocythemia (incl. platelet count increased), allergic reaction, dermatitis allergic, cerebral and intracranial hemorrhage, syncope, tachycardia, dry mouth, hepatic function abnormal, urticaria, hemarthrosis, feeling unwell (incl. malaise), increased bilirubin, increased blood alkaline phosphatase, increased LDH, increased lipase, increased amylase and increased GGT.

Rare
Jaundice, muscle hemorrhage, localized oedema, bilirubin conjugated increased (with or without concomitant increase of ALT), and vascular pseudoaneurysm.

## 4.8 Ability to drive and operate machine

Rivaroxaban has minor influence on the ability to drive and use machines. Patients experiencing adverse reactions like syncope and dizziness should not drive or use machines.

## 4.9 Overdose

**Symptoms:**
Overdose may lead to hemorrhagic complications. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50mg rivaroxaban or above.

**Treatment:**
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.

**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. Management should be individualized according to the severity and location of the hemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical

hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia or coagulopathy) or platelets. If bleeding cannot be controlled by the above measures, Re-dosing of recombinant Factor VIIa shall be considered and titrated depending on improvement of bleeding.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Mode of Action**

Rivaroxaban is a highly selective direct Factor Xa inhibitor. 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 has no effects on platelets.

### 5.2 Pharmacokinetic properties

Absorption:

Rivaroxaban is rapidly absorbed with maximum concentrations ($C_{max}$) appearing 2 – 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is high (80-100 %) for the 10mg dose irrespective of fasting/fed conditions. Absorption of rivaroxaban is dependent on the site of drug release in the GI 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 drug is released in the distal small intestine, or ascending colon.

Effect of Food

Oral bioavailability of Rivaroxaban 20mg tablet is reduced to 66% under fasting conditions. When Rivaroxaban 20mg tablet is taken with food mean AUC is increased by 39% compared to tablet taken under fasting conditions. This indicates almost complete absorption and high oral bioavailability. Rivaroxaban 10mg tablets can be taken with or without food. Rivaroxaban 15mg and 20mg tablets should be taken with food.

Distribution

Plasma protein binding is high at approximately 92% to 95%, with serum albumin being the main binding component. The volume of distribution is moderate with Vss (steady-state volume of distribution) being approximately 50 litres.

Metabolism

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Elimination
Following oral administration, approximately one-third of the absorbed dose is excreted unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and feces.

**Special population**

Patients with hepatic impairment
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.

Patients with renal impairment
In individuals with mild (creatinine clearance 50 – 80ml/min), moderate (creatinine clearance 30 – 49ml/min) and severe (creatinine clearance 15 – 29ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively.
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. Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable. 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of Excipients

- Lactose Monohydrate
- Microcrystalline Cellulose (Avicel PH-101)
- Methocel E-5 (HPMC 5 CPS)
- Sodium Lauryl Sulfate
- Croscarmellose Sodium
- Magnesium Stearate
- Pharmacoat 615 (15CPS)
- Titanium Dioxide
- P.E.G 3350 PF
- Ferric Oxide Red

### 6.2 Incompatibilities

None

6.3 **Shelf-life**

2 Years
The expiration date refers to the product correctly stored in the required conditions.

6.4 **Special precautions for storage**

- Do not store above 30°C.
- Protect from sunlight & moisture.
- The expiration date refers to the product correctly stored at the required conditions.

6.5 **Nature and contents of container**

Rivaxo (Rivaroxaban) Tablets 20mg are available in a Alu-Alu blister pack of 30's Tablets in a unit carton along with a package insert.

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

No special requirements.
- Keep out of reach and sight of children.
- To be sold on prescription of a registered medical practitioner only.

7. **MARKETING AUTHORISATION HOLDER**

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. **MARKETING AUTHORIZATION NUMBER**
H2024/CTD11125/24011

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
May 12th, 2016

10. **DATE OF REVISION OF THE TEXT**
May 12th, 2016