

(Rivaroxaban)



COMPOSITION
RIvaro 2.5mg Tablet:
Each film-coated tablet contains: Rivaroxaban 2.5mg
Rivaro 10mg Tablet:
Each film-coated tablet contains: Rivaroxaban 10mg
Rivaro 15mg Tablet:
Each film-coated tablet contains: Rivaroxaban 15mg

Rivaro 20mg Tablet:
Each film-coated tablet contains: Rivaroxaban 13mg

**DESCRIPTION**Rivaroxaban, a factor Xa (FXa) inhibitor, is the active ingredient in

### MECHANISM OF ACTION

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Rivaro (rivaroxaban) is a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

## PHARMACOKINETICS

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When given orally, rivaroxaban is rapidly absorbed and peak plasma concentration occurs after 2 to 4 hours. The bioavailability of rivaroxaban is dose dependent; it is about 80% to 100% for the 2.5 mg and 10 mg doses and is unaffected by food. With larger doses bioavailability is lower but is increased with food. Plasma protein binding is about 92% to 95%. Rivaroxaban is metabolized by the cytochrome P450 isoenzymes CYYP3A4 and CYP2J2 and by other mechanism. About two third of an oral dose is metabolized, with the metabolites excreted equally in the urine and feces; the remaining third is excreted unchanged in the urine, mainly by active renal secretion. After an intravenous dose of rivaroxaban the elimination half-life is about 4.5 hours, but on oral dosage elimination is limited by the rate of absorption and the terminal half-life is about 7 to 11 hours.

## INDICATIONS AND USAGE

- DICATIONS AND USAGE
  is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
  It is indicated for the treatment of deep vein thrombosis (DVT). It is indicated for the treatment of pulmonary embolism (PE). It is indicated for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

- and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.

  It is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery. In combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction and stroke) in patients with chronic coronary artery disease (CAD).

  In combination with aspirin, is indicated to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stoke, acute limb ischemia and major amputation of vascular etiology) in patients with peripheral artery disease (PAD), including patients with have recently undergone allower externity revascularization procedure due to symptomatic PAD.

  It is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolism complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding. It is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment. It is indicated for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

- aged 2 years and older with congenital neart disease who have undergone the Fontan procedure.

  DOSAGE AND ADMINISTRATION

  The dosage of Rivaroxaban in the following conditions are as;

  Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; the dosage is 20 mg once daily for the patient having CrCI more than 50 mL/min and 15 mg once daily for patient having CrCL ≤ 50 mL/min. It is to be taken with evening food.

  Initial treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); the dosage is 15 mg twice daily for 21 days in patient having CrCl ≥ 15 mL/min, lafter 21 days the dosage is 20 mg once daily, It should be taken with food. It should be avoided if CrCl is below 15 mL/min.

  Reduction in the risk of recurrence of DVT and/or PE; in patients at continued risk for recurrent DVT and/or PE; the dosage is 10 mg once, after at least six months of standard anticoagulant treatment, in patient having CrCl ≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min.

  Prophylaxis of venous thromboembolism, which may lead to PE in patients undergoing knee replacement surgery; the dosage is 10 mg once daily for 12 days, to be started 6 10 hours after surgery once hemostasis has been established in patient having CrCl ≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min.

  Prophylaxis of venous thromboembolism, which may lead to PE in patients undergoing knee replacement surgery; the dosage is 10 mg once daily for 12 days, to be started 6 10 hours after surgery once hemostasis has been established in patient having CrCl ≥ 15 mL/min.

  Prophylaxis of venous thromboembolism, which may lead to PE in patients undergoing knee replacement surgery once hemostasis has been established in patient having CrCl ≥ 15 mL/min.

- established in patient having CrCl ≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min. Prophylaxis of venous thromboembolism, which may lead to PE in patients undergoing hip replacement surgery; the dosage is 10 mg once daily for 5 weeks, to be started 6 10 hours after surgery once hemostasis has been established in patient having CrCl ≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min. Reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD)); the dosage is 2.5 mg twice dally, plus asplirin (75 mg − 100 mg) once daily. It can be taken with or without food. No dose adjustment is needed based on CrCl. Reduce the risk of major thrombotic vascular events in PD, including patients after lower extremity revascularization due to symptomatic PAD; the dosage is 2.5 mg twice daily, plus asplirin (75 mg − 100 mg) once daily. It can be taken with or without food. No dose adjustment is needed based on CrCl. When starting therapy after a successful lower extremity revascularization procedure, initiate once hemostasis has been established.

  Prophylaxis of VTE in acutely III medical patients at risk for thromboembolic complications not at high risk of bleeding; the dosage is 10mg once daily in hospital and after hospital discharge for a total recommended duration of 31 to 39 days in patient having CrCl ≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min.
- 39 days in patient having CrCl≥ 15 mL/min. It can be taken with or without food. It should be avoided if CrCl is below 15 mL/min.

  In pediatric patients the dosage for the treatment of venous thromboembolism and reduction in risk of recurrent venous thromboembolism birth to less than 18 years of age are;

  Body weight 2.6 kg to 2.9 kg: the recommended dose is 0.8 mg three times a day. The maximum total daily dose is 2.4 mg Body weight 3kg to 3.9 kg: the recommended dose is 0.9 mg three times a day. The maximum total daily dose is 2.7 mg Body weight 14 kg to 4.9 kg: the recommended dose is 1.4 mg Body weight 15 kg to 6.9 kg: the recommended dose is 1.4 mg Body weight 15 kg to 6.9 kg: the recommended dose is 1.6 mg Body weight 17 kg to 7.9 kg: the recommended dose is 1.8 mg Body weight 18 kg to 8.9 kg: the recommended dose is 2.4 mg Body weight 18 kg to 8.9 kg: the recommended dose is 2.4 mg Body weight 19 kg to 9.9 kg: the recommended dose is 2.8 mg Body weight 10 kg to 1.1 kg: the recommended dose is 2.8 mg Body weight 10 kg to 1.1 kg: the recommended dose is 2.8 mg three times a day. The maximum total daily dose is 8.4 mg Body weight 10 kg to 1.1 kg: the recommended dose is 5.9 mg three times a day. The maximum total daily dose is 8.9 mg three times a day. The maximum total daily dose is 5.0 mg body weight 10 kg to 1.1 kg: the recommended dose is 5 mg body weight 30 kg to 48 yg: the recommended dose is 5 mg body weight 30 kg to 48 yg: the recommended dose is 5 mg body weight more than or equal to 50 kg: the recommended dose is 15 mg body weight more than or equal to 50 kg: the recommended dose is 15 mg body weight more than or equal to 50 kg: the recommended dose is 15 mg body weight more than or equal to 50 kg: the recommended dose in 10 mg Body weight more than or equal to 50 kg: the recommended dose in 10 mg Body weight more than or equal to 50 kg: the recommended dose in 10 mg Body weight more than or equal to 50 kg: the recommended dose in 10 mg Body weight more than or equal to 50 kg: the recommended dos

is zU mg once a day. The maximum total daily dose is 20 mg Its use is not recommended in children less than 6 months of age with any of the following:

o Less than 37 weeks of gestation at birth

Less than 10 days of oral feeding

o Body weight of less than 2.6 kg.

To increase absorption, all doses should be taken with feeding or with food. Monitor the child's weight and review the dose regularly, especially for children below 12 kg. This is to ensure a therapeutic dose is maintained.

oose is maintained.

All pediatric patients (except <2 years old with catheter-related thrombosis): Therapy with rivaroxaban should be continued for at least 3 months in children with thrombosis. Treatment can be extended up to 12 months when clinically necessary. The benefit of continued therapy beyond 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential risk of bleeding.

Pediatric patients <2 years old with catheter-related thrombosis: Therapy with rivaroxaban should be continued for at least 1 month in children less than 2 years old with catheter-related thrombosis. Treatment can be extended up to 3 months when clinically necessary. The benefit of continued therapy beyond 1 month should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential risk of bleeding.

- the potential risk of bleeding.

  In pediatric patients the dosage for the treatment of thromboprophylaxis with congenital heart disease after the Fontan procedure are;
  Body weight 7 kg to 7.9 kg: the recommended dose is 1.1 mg two times a day. The maximum total daily dose is 2.2 mg
  Body weight 8 kg to 9.9 kg: the recommended dose is 1.6 mg two times a day. The maximum total daily dose is 3.2 mg
  Body weight 10 kg to 11.9 kg: the recommended dose is 1.7 two times a day. The maximum total daily dose is 3.4 mg
  Body weight 12 kg to 19.9 kg: the recommended dose is 2.5 mg two times a day. The maximum total daily dose is 4 mg
  Body weight 20 kg to 29.9 kg: the recommended dose is 2.5 mg two times a day. The maximum total daily dose is 5 mg
  Body weight 30 kg to 49.9 kg: the recommended dose is 7.5 mg
  Body weight 30 kg to 49.9 kg: the recommended dose is 7.5 mg
  Gore a day. The maximum total daily dose is 5 mg
  Body weight more than or equal to 50 kg: the recommended dose is 10 mg once aday. The maximum total daily dose is 10 mg
  For the treatment of VTE in children, the dose should be taken with food to increase absorption. For thromboprophylaxis after Fontan procedure, the dose can be taken with or without food. If the patient vomits or spits up the dose within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits or spits up the dose repeatedly, the caregiver should contact the child's doctor right away.

  Use in Renal Impairment in Pediatric Patients
  Patients 1 venue for accordance.

- Use in Renal Impairment in Pediatric Patients
  Patients 1 year of age or older

  Mild renal impairment (eGFR: 50 to 80 mL/min/1.73 m²): No dose adjustment is required.
- Moderate or severe renal impairment (eGFR: <50 mL/min/1.73 m²): avoid use, as limited clinical data are available

Patients Less than 1 Year of Age
Determine renal function using serum creatinine. Avoid use of rivaroxaban in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

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

Switching from rivaroxaban to warfarir. No clinical data are available to guide converting patients from rivaroxaban to warfarin. Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin.

Switching from rivaroxaban to warfarin in adult; To ensure adequate anticoagulation during the transition from rivaroxaban to warfarin, continue it for at least 2 days after the first dose of warfarin. After 2 days of co-administration, an INR should be obtained prior to the next scheduled dose of rivaroxaban.

Co-administration of rivaroxaban and warfarin is advised to continue until the INR is  $\geq$  2.0. Once rivaroxaban is discontinued, INR testing may be done reliably 24 hours after the last dose.

INR testing may be done reliably 24 hours after the last dose. Switching from rivaroxaban to anticoagulants other than warfarin; For patients currently taking rivaroxaban and transitioning to an anticoagulant with rapid onset, discontinue rivaroxaban and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next rivaroxaban dose would have been taken. Switching from anticoagulants other than warfarin to rivaroxaban; For patients currently receiving an anticoagulant other than warfarin, start rivaroxaban 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start rivaroxaban at the same time.

Discontinuation for surgery and other interventions
If anticoagulation must be discontinued to reduce the risk of
bleeding with surgical or other procedures, rivaroxaban should be
stopped at least 24 hours before the procedure to reduce the risk
of bleeding. In deciding whether a procedure should be delayed
until 24 hours after the last dose or irvaroxaban, the increased risk
of bleeding should be weighed against the urgency of intervention.
Rivaroxaban should be restarted after the surgical or other
procedures as soon as adequate hemostasis has been
established. If oral medication cannot be taken during or after
surgical intervention, consider administering a parenteral
anticoagulant.

- Missed dose in adults
  For patients receiving 2.5 mg twice daily: if a dose is missed, the patient should take a single 2.5 mg rivaroxaban dose as recommended at the next scheduled time.
  For patients receiving 15 mg twice daily: The patient should take rivaroxaban immediately to ensure intake of 30 mg rivaroxaban per day.

  For patients receiving 20 mg. 15 mg or 10 mg once daily: The
- For patients receiving 20 mg, 15 mg or 10 mg once daily. The patient should take the missed rivaroxaban dose immediately. The dose should not be doubled within the same day to make up for a missed dose.

- Missed dose in pediatrics

  If it is taken once a day, the patient should take the missed dose as soon as possible once it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.
- cose.

  If it is taken two times a day, the patient should take the missed morning dose as soon as possible once it is noticed. A missed morning dose may be taken together with the evening dose, A missed evening dose can only be taken in the same
- If it is taken three times a day, if a dose is missed, the patient should skip the missed dose and go back to the regular dosing schedule at the usual time without compensating for the missed dose.

On the following day, the patient should continue with their regular

Administration options
For patients who are unable to swallow whole tablets, rivaroxaban tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed rivaroxaban 15 mg or 20 mg 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, rivaroxaban tablest may be crushed and suspended in 50 mL of water an administered via an NG tube or gastric feeding tube. After the administration of a crushed rivaroxaban 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding.

ADVERSE REACTIONS
The reported adverse events of rivaroxaban are; increased risk of stroke after discontinuation in nonvalvular atrial fibrillation, bleeding risk, spinal / epidural hematoma, Intracranial bleeding (included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma), hemorrhagic stroke (non-traumatic intraparenchymal and/or intraventricular hematoma), gastrointestinal bleeding (included upper GI, lower GI, and rectal bleeding), fatal bleeding (is adjudicated death with the primary cause of death from bleeding), non-fatal critical organ bleeding (intracranial, retropertioneal, intracouclar, intra-articular), decrease in hemoglobin, extra surgical site bleeding, hemorrhagic stroke, abdominal pain, fatigue, back pain, muscle spasm, dizziness, anxiety, depression, insomnia, pruritus, wound secretion, pain in extremity, syncope, blister, pulmonary hemorrhage, pulmonary hemorrhage with bronchiectasis, anemia, diarrhea, constipation, fever, headache, hypotension, menorrhagia, nausea, edma, renal impairment, skin reactions, vomiting, angloedema, dry mouth, hepatic disorder, malaise, tachycardia, thrombocytopenia and thrombocytosis. The additional reported adverse events are agranulocytosis, thrombocytopenia, retroperitioneal hemorrhage, jaundice, cholestasis, hepatitis (including hepatocellular injury), hypersensitivity, anaphylactic reaction, anaphylactic shock, angioedema, cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS).

DRUG INTERACTIONS
General inhibition and induction properties
Rivaroxaban is a substrate of CYP3A4/15, CYP2J2, and the P-gp
and ATP-binding cassette 62 (ABC62) transporters. Combined
P-gp and strong CYP3A inhibitors increase exposure to
rivaroxaban and may increase the risk of bleeding. Combined
P-gp and strong CYP3A inducers decrease exposure to
rivaroxaban and may increase the risk of thromboembolic events.

# Drugs that inhibit cytochrome P450 3A enzymes and drug

Drugs that inhibit cytochrome P450 3A enzymes and drug transport systems Interaction with Combined P-gp and Strong CYP3A Inhibitors. Avoid concomitant administration of rivaroxaban with known combined P-gp and strong CYP3A inhibitors (e.g., ketoconazole and ritonavir). Although darithromycin is a combined P-gp and strong CYP3A inhibitor, pharmacokinetic data suggests that no precautions are necessary with concomitant administration with rivaroxaban as the change in exposure is unlikely to affect the bleeding risk.

bleeding risk.

Interaction with Combined P-gp and Moderate CYP3A Inhibitors in Patients with Renal Impairment.

Rivaroxaban should not be used in patients with CrCl 15 to < 80 mL/min who are receiving concomitant combined P-gp and moderate CYP3A inhibitors (e.g., erythromycin) unless the potential benefit justifies the potential risk.

Drugs that induce cytochrome P450 3A enzymes and drug transport systems
Avoid concomitant use of rivaroxaban with drugs that are combined P-pg and strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort).

Anticoagulants and NSAIDs / Aspirin
Coadministration of enoxaparin, warfarin, aspirin, clopidogrel and chronic NSAID use may increase the risk of bleeding. Avoid concurrent use of rivaroxaban with other anticoagulants due to increased bleeding risk unless benefit outweighs risk. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

### CONTRAINDICATIONS

- varoxaban is contraindicated in patients with: Active pathological bleeding (in acute coronary syndrome; previous stroke and transient ischemic attack, malignant neoplasm, esophageal varices, recent brain surgery, recent gastrointestinal ulcer, recent intracranial hemorrhage, recent ophthalmic surgery, recent spine surgery, significant risk of major bleeding, vascular aneurysm.
- Severe hypersensitivity reaction to rivaroxaban (e.g., anaphylactic reactions).

USE IN SPECIFIC POPULATIONS
Pregnancy
The limited available data on rivaroxaban in pregnant women are insulficient to inform a drug-associated risk of adverse developmental outcomes. Use rivaroxaban with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery. Consider the benefits and risks of rivaroxaban for the mother and possible risks to the fetus when prescribing rivaroxaban to a pregnant woman.

Disease-Associated Maternal and/or Embryo/Fetal Risk Pregnancy is a risk factor for venous thromboembolism and trisk is increased in women with inherited or acqui thrombophilias. Pregnant women with thromboembolic disea have an increased risk of maternal complications include pre-edampsia. Maternal thromboembolic disease increases risk for intrauterine growth restriction, placental abruption a early and late pregnancy loss.

Fetal/Neonatal Adverse Reactions
Based on the pharmacologic activity of Factor Xa inhibitors and the potential to cross the placenta, bleeding may occur at any site in the fetus and/or neonate.

# Labor or Delivery All patients receiving anticoagulants, including pregnant women, are at risk for bleeding and this risk may be increased during labor or delivery.

or delivery.

Lactation
Rivaroxaban has been detected in human milk. There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for rivaroxaban and any potential adverse effects on the breastfed infant from rivaroxaban or from the underlying maternal condition. Females and males of reproductive potential. Females or reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Pediatric Use Safety and effectiveness in pediatric patients have not been established. Geriatric Use
The efficacy of rivaroxaban in the elderly (65 years or older) was
through the to that seen in patients younger than 65 years. Both
thrombotic and bleeding event rates were higher in these older
patients, but the risk-benefit profile was favorable in all age
groups.

Renal Impairment
Nonvalvular Atrial Fibrillation
Patients with chronic kidney disease not on dialysis Patients with
CrCl ≤30 mL/min were not studied, but administration of
rivaroxaban 15 mg once daily is expected to result in serum
concentrations of rivaroxaban similar to those in patients with

moderate renal impairment.
Patients with end-stage renal disease on dialysis Clinical efficacy
and safety studies with rivaroxaban in patients with end-stage
renal disease (ESRD) on dialysis was not carried out.

Treatment of DVT and/or PE and reduction in the risk of recurrence of DVT and/or PE.

Avoid the use of rivaroxaban in patients with CrCl <30 mL/min. Prophylaxis of DVT following Hip or Knee Replacement Surgery
Avoid the use of rivaroxaban in patients with CrCl <30 mL/min.

Avoid the use of nivaroxaban in patients with CrCl <30 mLmm. Reduction of Risk of Major Cardiovascular Events in Patients with Chronic CAD or PAD Patients with Chronic Kidney Disease not on Dialysis in patients with CrCl <30 mL/min, a dose of 2.5 mg rivaroxaban twice daily is expected to give an exposure similar to that in patients with moderate renal impairment, whose efficacy and safety outcomes were similar to those with preserved renal function. Patients with End-Stage Renal Disease on Dialysis No clinical outcome data is available for the use of rivaroxaban with aspirin in patients with ESRD on dialysis.

WARNINGS AND PRECAUTIONS
Increased risk of thrombotic events after discontinuation
Premature discontinuation of any oral anticoagulant, including rivaroxaban, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

with another anticoagulant.

Risk of bleeding
Rivaroxaban increases the risk of bleeding and can cause serious
or fatal bleeding. In deciding whether to prescribe rivaroxaban to
patients at increased risk of bleeding, the risk of thrombotic events
should be weighed against the risk of bleeding. Promptly evaluate
any signs or symptoms of blood loss and consider the need for
blood replacement. Discontinue rivaroxaban in patients with active
pathological hemorrhage. Concomitant use of other drugs that
impair hemostasis increases the risk of bleeding. These include
aspirin, P2Y12 platelet inhibitors, dual antiplatelet therapy, other
antithrombotic agents, fibrinolytic therapy, non-steroidal
anti-inflammatory drugs (NSAIDs), selective serotonin reuptake
inhibitors, and serotonin norepinephrine reuptake inhibitors.
Concomitant use of drugs that are known combined P-gp and
strong CYP3A inhibitors increases rivaroxaban exposure and may
increase bleeding risk. ling risk.

increase bleeding risk.

Reversal of Antiooagulant Effect.

An agent to reverse the anti-factor Xa activity of rivaroxaban is available. Because of high plasma protein binding, rivaroxaban is not dialyzable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. Use of procoagulant reversal agents, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa, may be considered. Monitoring for the anticoagulation effect of rivaroxaban using a clotting test (PT, INR or aPTT) or anti-factor Xa (FXa) activity is not recommended.

Spinal / Epidural anesthesia or puncture
When neuraxial anesthesia (spinal/epidural anesthesia) or spinal
puncture is employed, patients treated with anticoagulant 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.

An indwelling epidural or intrathecal catheter should not be
removed (i.e., 18 hours in young patients aged 20 to 45 years and
26 hours in elderly patients aged 60 to 76 years), after the last
administration of rivaroxaban. The next rivaroxaban dose should
not be administered earlier than 6 hours after the removal of the
catheter. If traumatic puncture occurs, delay the administration of
rivaroxaban for 24 hours.
Should the physician decide to administer anticoagulation in the
context of epidural or spinal anesthesia/analgesia or lumbar
puncture, monitor frequently to detect any signs or symptoms of
neurological impairment, such as midline back pain, sensory and
motor deficits (numbness, tingling, or weakness in lower limbs),
bowel and/or bladder dysfunction. Instruct patients to immediately
report if they experience any of the above signs or symptoms. If
signs or symptoms of spinal hematoma are suspected, initiate
urgent diagnosis and treatment including consideration for spinal
cord decompression even though such treatment may not prevent
or reverse neurological sequelae.

Use in patients with renal impairment

Nonvalvular Atrial Fibrillation.

Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Consider dose adjustment or discontinuation of rivaroxaban in patients who develop acute renal failure while on trivaroxaban.

fallure while on rivaroxaban.
Treatment of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), and Reduction in the Risk of Recurrence of DVT and of PE Avoid the use of rivaroxaban in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure.

to an expected increase in rivaroxaban exposure. 

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery. 
Avoid the use of rivaroxaban in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min. Patients who develop acute renal failure while on rivaroxaban should discontinue the treatment.

Prophylaxis of Venous Thromboembolism in Acutely III Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding
In patients with CrCl <30 mL/min, rivaroxaban exposure and pharmacodynamic effects are increased compared to patients with normal renal function. There are limited clinical data in patients with CrCl 15 to <30 mL/min, therefore, observe closely and promptly evaluate any signs or symptoms of blood loss in these patients. There are no clinical data in patients with CrCl 15 mL/min (including patients on dialysis); therefore, avoid the use of it in these patients. Discontinue rivaroxaban in patients who develop acute renal failure while on treatment. Pediatric Patients; There are limited clinical data in pediatric patients 1 year or older with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m²); therefore, avoid the use of it in these patients.

patients. There are no clinical data in pediatric patients younger than 1 year with serum creatinine results above 97.5° percentile; therefore, avoid the use of rivaroxaban in these patients.

Use in patients with hepatic impairment
Avoid use of rivaroxaban in patients with moderate (Child-Pugh B)
and severe (Child-Pugh C) hepatic impairment or with any hepatic
disease associated with coagulopathy since drug exposure and
bleeding risk may be increased.
No dinical data are available for adult patients with severe hepatic
impairment. No clinical data are available in pediatric patients with
hepatic impairment.

Use with P-gp and strong CYP3A inhibitors or inducers Avoid concomitant use of rivaroxaban with known combined P-gp

Avoid concomitant use of rivaroxaban with known combined P-gp and strong CYP3A inhibitors. Avoid concomitant use of rivaroxaban with drugs that are known combined P-gp and strong CYP3A inducer.

Risk of pregnancy-related hemorrhage
In pregnant women, rivaroxaban should be used only if the potential benefit justifies the potential risk to the mother and fetus. Rivaroxaban dosing in pregnancy has not been studied. The anticoagulant effect of rivaroxaban cannot be monitored with standard laboratory testing. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

# Patients with prosthetic heart valves The safety and efficacy of rivaroxaban have not been studied in patients with prosthetic heart valves. Therefore, use of rivaroxaban is not recommended in these patients.

Acute PE in hemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy Initiation of rivaroxaban is not recommended acutely as an alternative to unfractionated heparin in patients with pulmonary embolism who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Increased risk of thrombosis in patients with antiphospholipid syndrome Direct-acting oral anticoagulants (DOACs), including rivaroxaban are not recommended for use in patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti-beta 2-glycoprotein I antibodies)], treatment with DOACs has been associated with an increased rate of recurrent thrombotic events compared with vitamin K antagonist therapy. Rivaroxaban should not be used as alternative to unfractionated heparin in pulmonary embolism in patients with hemodynamic instability, or who may receive thrombolysis or pulmonary embolectomy, severe hypertension and vascular retinopathy.

## OVERDOSAGE

OVERDOSAGE

Overdose of rivaroxaban may lead to hemorrhage. Discontinue rivaroxaban and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not dialyzable. Partial reversal of laboratory anticoagulation parameters may be achieved with use of plasma products. An agent to reverse the anti-factor Xa activity of rivaroxaban is available.

DOSAGE AND INSTRUCTIONS
To be sold and used on the pro-To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Rivaro 2.5mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.
Rivaro 10mg Tablets: Alu. Alu. Blister Pack of 1 x 10's.
Rivaro 15mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.
Rivaro 20mg Tablets: Alu. Alu. Blister Pack of 1 x 14's.

خوراک و ہدایات: صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعال کی جائے۔ یوں کی پینچ سے دور رکھیں۔ ℃30 سے زیادہ درجہ حرارت پر ندر کھیں۔ خشک جگہ پر رکھیں۔ روشنی سے بحایئیں۔

Manufactured by HIGHNOON LABORATORIES LTD 17.5 KM, Multan Road, Lahore, Pakistan. www.biahnoon-labs.com

Item Code No. 14002835