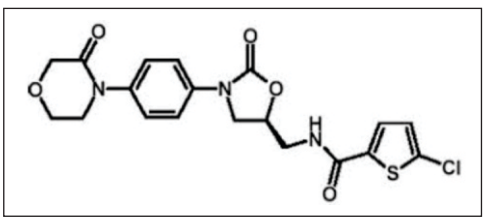
RIVASCOT
Tablets*

ریواسکاٹ ٹیبلٹس

COMPOSITION:
Each Film coated tablet contains:
Rivaroxaban.....10,15 & 20 mg*

WARNINGS: (A) DISCONTINUING RIVASCOT IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA
A. DISCONTINUING RIVASCOT IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION
Discontinuing RIVASCOT places patients at an increased risk of thrombotic events. If anticoagulation with RIVASCOT must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
B. SPINAL/EPIDURAL HEMATOMA
Epidural or spinal hematomas have occurred in patients treated with RIVASCOT who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis)
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.

DESCRIPTION
Rivaroxaban, a factor Xa inhibitor, is the active ingredient in RIVASCOT Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5 yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is C19H18ClN3O5S and the molecular weight is 435.89. The structural formula is:



CLINICAL PHARMACOLOGY:
Mechanism of Action: RIVASCOT is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

Pharmacodynamics: Dose-dependent inhibition of factor Xa activity is observed in humans and the Neoplastin prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest are prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban

Pharmacokinetics:

Absorption
The absolute bioavailability of rivaroxaban is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. RIVASCOT 10 mg tablets can be taken with or without food
The maximum concentrations (Cmax) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban is not affected by drugs altering gastric pH. Coadministration of RIVASCOT with the H2-receptor antagonist ranitidine,the antacid aluminum hydroxide/magnesium hydroxide or RIVASCOT with the PPI omeprazole do not show an effect on the bioavailability and exposure of rivaroxaban.

Distribution
Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism
Approximately 51% of an orally administered rivaroxaban dose is recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban is the predominant moiety in plasma with no major or active circulating metabolites.

Excretion
Following oral administration of a rivaroxaban dose, 66% of the radioactive dose is recovered in urine (36% as unchanged drug) and 28% is recovered in feces (7% as unchanged). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

INDICATIONS AND USAGE
Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation
RIVASCOT (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Prophylaxis of Deep Vein Thrombosis
RIVASCOT (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

CONTRAINDICATIONS
RIVASCOT is contraindicated in patients with:
- Active pathological bleeding.
- Severe hypersensitivity reaction to RIVASCOT.

DRUG INTERACTIONS
Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.
Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems
Avoid concomitant administration of RIVASCOT with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.
Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems
Avoid concomitant use of RIVASCOT with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin St. John's wort).
Anticoagulants
Single doses of enoxaparin and RIVASCOT (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin do not affect the pharmacokinetics of rivaroxaban. Single doses of warfarin and RIVASCOT resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban.
NSAIDs/Aspirin
NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with RIVASCOT.
Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors or NSAIDs
Clopidogrel
Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with clopidogrel.
Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems
Renal impairment receiving full dose RIVASCOT in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin and azithromycin) may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

ADVERSE REACTIONS
Hemorrhage
The most common adverse reactions with RIVASCOT are bleeding complications.
Nonvalvular Atrial Fibrillation
The most frequent adverse reactions associated with permanent drug discontinuation are bleeding events.
Prophylaxis of Deep Vein Thrombosis
The most common adverse reaction with RIVASCOT is Deep Vein Thrombosis.
Other Adverse Reactions
Non-hemorrhagic adverse drug reactions (ADRs)
Acute medically ill patients being treated with RIVASCOT

10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis may occur.

WARNINGS AND PRECAUTIONS

Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation

Discontinuing RIVASCOT in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. If RIVASCOT must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.

Risk of Bleeding

RIVASCOT increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe RIVASCOT 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. Discontinue RIVASCOT in patients with active pathological hemorrhage.

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 epidural catheter should not be removed earlier than 18 hours after the last administration of RIVASCOT. The next RIVASCOT dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of RIVASCOT is to be delayed for 24 hours.

Risk of Pregnancy Related Hemorrhage

RIVASCOT should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. RIVASCOT dosing in pregnancy has not been studied. The anticoagulant effect of RIVASCOT cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension or fetal distress).

Severe Hypersensitivity Reactions

There are cases of anaphylaxis in patients treated with RIVASCOT to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction to RIVASCOT should not receive RIVASCOT.

SPECAIL POPULATIONS

Pregnancy

Pregnancy Category C

Use RIVASCOT with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible.

Nursing Mothers

It is not known if rivaroxaban is excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue RIVASCOT, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Both thrombotic and bleeding event rates are higher in older patients, but the risk-benefit profile is favorable in all age groups.

Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

Renal impairment: Patients with renal impairment taking P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk

Hepatic Impairment

Avoid the use of RIVASCOT in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy.

DOSAGE AND ADMINISTRATION

Nonvalvular Atrial Fibrillation: For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of RIVASCOT is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal

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

Switching from or to Anticoagulants other than Warfarin: For patients currently receiving an anticoagulant other than warfarin, start RIVASCOT 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 RIVASCOT at the same time.

Prophylaxis of Deep Vein Thrombosis: The recommended dose of RIVASCOT is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

Hip Replacement Surgery: For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.

Knee Replacement Surgery: For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

OVERDOSE

Overdose of RIVASCOT may lead to hemorrhage. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. Discontinue RIVASCOT and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of RIVASCOT overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 °C. Keep all medicines out of the reach of children. To be sold and used on the prescription of Registered Medical Practitioners.

PRESENTATION: RIVASCOT Tablets 10,15 & 20 mg is available in packing containing 10 film coated tablets.

*Scotmann Specs.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

Complete Medical Information available only for doctors on request.

scotmann

Manufactured by: **SCOTMANN PHARMACEUTICALS**
5-D, I-10/3 Industrial Area, Islamabad-Pakistan.
www.scotmann.com