ARIXA

[Rivaroxaban]

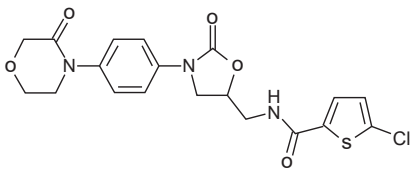
ایرِگزا

Tablets 10 mg, 15 mg & 20 mg

DESCRIPTION

Rivaroxaban, a factor Xa inhibitor, is the active ingredient in ARIXA 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 $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89.

The structural formula is:



Rivaroxaban is a pure (S)-enantiomer. It is an odorless, non-hygroscopic, and white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

QUALITATIVE & QUANTITATIVE COMPOSITION

ARIXA (Rivaroxaban) is available for oral administration as:

1. ARIXA Tablets 10 mg
Each film-coated tablet contains:
Rivaroxaban….10 mg

2. ARIXA Tablets 15 mg
Each film-coated tablet contains:
Rivaroxaban….15 mg

3. ARIXA Tablets 20 mg
Each film-coated tablet contains:
Rivaroxaban….20 mg

CLINICAL PHARMACOLOGY

Mechanism of Action

ARIXA 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.

Pharmacodynamic

Dose-dependent inhibition of factor Xa activity was 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. ARIXA 10 mg tablets can be taken with or without food.
The absolute bioavailability of rivaroxaban at a dose of 20 mg in the fasted state is approximately 66%. Co-administration of ARIXA with food increases the bioavailability of the 20 mg dose (mean AUC and Cmax increasing by 39% and 76% respectively with food).
ARIXA 15 mg and 20 mg tablets should be taken with the evening meal.
The maximum concentrations (Cmax) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and Cmax 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. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure.

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 [14C]-rivaroxaban dose was 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 was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

Following oral administration of a [14C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). 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 affinity for influx transporter proteins is unknown. Rivaroxaban is a low clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Special Populations

Gender

Gender did not influence the pharmacokinetics or Pharmacodynamic of ARIXA.

Race

Healthy Japanese subjects were found to have 20 to 40% on average, higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly

In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to reduced (apparent) total body and renal clearance. Age related changes in renal function may play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly.

Body Weight

Extremes in body weight (<50 kg or >120 kg) did not influence (less than 25%) rivaroxaban exposure.

THERAPEUTIC INDICATIONS

ARIXA (Rivaroxaban) is indicated for the treatment of:
Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation
• To reduce the risk of stroke and systemic embolism in patients with Nonvalvular Atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis

• For the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

DOSAGE & ADMINISTRATION

Nonvalvular Atrial Fibrillation
For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of ARIXA 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 ARIXA, discontinue warfarin and start ARIXA 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 ARIXA 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 ARIXA at the same time.

Prophylaxis of Deep Vein Thrombosis
The recommended dose of ARIXA 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.
• For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
• For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

Hepatic impairment (for nonvalvular AF and prophylaxis of DVT indications):
Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any degree of hepatic disease associated with coagulopathy.

Missed Dose If a dose of ARIXA is not taken at the scheduled time, administer the dose as soon as possible on the same day.

ADVERSE REACTIONS
Hemorrhage: The most common adverse reaction (>5%) was bleeding.
Other Adverse Reactions: Non-hemorrhagic adverse drug reactions (ADRs) reported in ≥1% of ARIXA-treated patients

CONTRAINDICATIONS
ARIXA (Rivaroxaban) is contraindicated in patient with:
• In patient with active pathological bleeding
• In patient with severe hypersensitivity reaction to ARIXA

WARNING & PRECAUTIONS
Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation
Discontinuing ARIXA in the absence of adequate alternative anticoagulation increases the risk of thrombotic events.

Risk of Bleeding
Promptly evaluate any signs or symptoms of blood loss. Discontinue ARIXA in patients with active pathological hemorrhage.

Spinal/Epidural Anesthesia or Puncture
An epidural catheter should not be removed earlier than 18 hours after the last administration of ARIXA. The next ARIXA dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of ARIXA is to be delayed for 24 hours.

Risk of Pregnancy Related Hemorrhage
ARIXA should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus.

Severe Hypersensitivity Reactions
Patients who have a history of a severe hypersensitivity reaction to ARIXA should not receive ARIXA

DRUG INTERACTIONS
Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems
Avoid concomitant administration of ARIXA 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 ARIXA with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort).

Anticoagulants
Avoid concurrent use of ARIXA with other anticoagulants due to the increased bleeding risk.
Promptly evaluate any signs or symptoms of blood loss.

NSAIDs/Aspirin
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

USE IN SPECIFIC POPULATIONS
Pregnancy:
Pregnancy Category C
There are no adequate or well-controlled studies of ARIXA in pregnant women, and dosing for pregnant women has not been established. Use ARIXA 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.

Labor and Delivery: Safety and effectiveness of ARIXA during labor and delivery have not been studied in clinical trials.

Nursing mothers: Discontinue nursing or discontinue ARIXA, 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 were higher in these older patients, but the risk benefit profile was favorable in all age groups

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

Renal impairment: Prophylaxis of Deep Vein Thrombosis: Avoid use in patients with severe impairment

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

OVERDOSAGE
Discontinue ARIXA and initiate appropriate therapy if bleeding complications associated with over dosage occur. The use of activated charcoal to reduce absorption in case of ARIXA overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable.

STORAGE
Store at 25°C.Excursions permitted between 15°C to 30°C
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions

HOW SUPPLIED
• ARIXA 10 mg tablet are available in blister packs of 10's
• ARIXA 15 mg tablet are available in blister packs of 14's
• ARIXA 20 mg tablet are available in blister packs of 14's

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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ہدایات:
دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

SCILIFE

Manufactured by:
Scilife Pharma (Pvt.) Ltd.,
FD-57/58-A2, Korangi Creek Industrial Park (KCIP), Karachi - Pakistan