CLOXIPA Tablets
(Apixaban)

کلوکزیپا ٹیبلیٹس
(ایپکزابان)

WARNING:

A) PREMATURE DISCONTINUATION OF CLOXIPA INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including **Cloxipa**, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if **Cloxipa** is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with **Cloxipa** who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

COMPOSITION:

Cloxipa 2.5mg Tablet
Each film coated tablet contains:
Apixaban …….. 2.5mg
[Innovator's Specs.]

Cloxipa 5mg Tablet
Each film coated tablet contains:
Apixaban …….. 5mg
[Innovator's Specs.]

DESCRIPTION: Cloxipa (Apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4 methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide.

INDICATIONS: Cloxipa is indicated for the Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery, Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as prior stroke or transient ischaemic attack; age ≤ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Treatment of deep vein thrombosis and pulmonary embolism. Prevention of recurrent deep vein thrombosis and pulmonary embolism in adults.

DOSAGE AND ADMINISTRATION:

Recommended Dose:

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation: The recommended dose of **Cloxipa** for most patients is 5mg taken orally twice daily. The recommended dose of **Cloxipa** is 2.5mg twice daily in patients with at least two of the following characteristics:

- Age greater than or equal to 80 years.
- Body weight less than or equal to 60 kg.
- Serum creatinine greater than or equal to 1.5mg/dL.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery: The recommended dose of **Cloxipa** is 2.5mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of Deep Vein Thrombosis and Pulmonary Embolism: The recommended dose of **Cloxipa** is 10mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5mg taken orally twice daily.

Reduction in the Risk of Recurrence of Deep Vein Thrombosis and Pulmonary Embolism: The recommended dose of **Cloxipa** is 2.5mg taken orally twice daily after at least 6 months of treatment for Deep Vein Thrombosis or Pulmonary Embolism.

Missed Dose: If a dose of **Cloxipa** is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Temporary Interruption for Surgery and Other Interventions: Cloxipa should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. **Cloxipa** should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping **Cloxipa** and prior to the intervention is not generally required. **Cloxipa** should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Converting from or to Cloxipa:

Switching from warfarin to Cloxipa: Warfarin should be discontinued and **Cloxipa** started when the international normalized ratio (INR) is below 2.0.

Switching from Cloxipa to warfarin: Cloxipa affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue **Cloxipa** and begin both a parenteral anticoagulant and warfarin at the time the next dose of **Cloxipa** would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from Cloxipa to anticoagulants other than warfarin (oral or parenteral): Discontinue **Cloxipa** and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of **Cloxipa**.

Switching from anticoagulants other than warfarin (oral or parenteral) to Cloxipa: Discontinue the anticoagulant other than warfarin and begin taking **Cloxipa** at the usual time of the next dose of the anticoagulant other than warfarin.

Combined P-gp and Strong CYP3A4 Inhibitors: For patients receiving **Cloxipa** doses of 5mg or 10mg twice daily, reduce the dose by 50% when **Cloxipa** is coadministered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, itraconazole, ritonavir).

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In patients already taking 2.5mg twice daily, avoid coadministration of **Cloxipa** with combined P-gp and strong CYP3A4 inhibitors.

Administration Options: For patients who are unable to swallow whole tablets, 5mg and 2.5mg **Cloxipa** tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally. **Cloxipa** tablets may be crushed and suspended in 60ml of water or D5W and promptly delivered through a nasogastric tube.

CLINICAL PHARMACOLOGY: Mechanism of Action: Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.
Pharmacokinetics: Absorption: The absolute bioavailability of Apixaban is approximately 50% for doses up to 10mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10mg. At doses. 25mg Apixaban displays dissolution limited absorption with decreased bioavailability.
Distribution: Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.
Metabolism: Approximately 25% of an orally administered Apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Unchanged Apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.
Elimination: Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of Apixaban in the feces. Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

CONTRAINDICATIONS:
Apixaban Tablets are contraindicated in patients with the following conditions:
- Active pathological bleeding.
- Severe hypersensitivity reaction to Apixaban Tablets (e.g., anaphylactic reactions).

WARNINGS AND PRECAUTIONS:
- Apixaban Tablets can cause serious, potentially fatal, bleeding. Promptly evaluate signs and symptoms of blood loss. An agent to reverse the anti-factor Xa activity of Apixaban is available.
- Prosthetic heart valves.
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome.

SIDE EFFECTS:
Following are the side effects as described below:
- Chest pain or tightness
- Swelling of your face or tongue
- Trouble breathing or wheezing
- Feeling dizzy or faint

DRUG INTERACTIONS: Inhibitors of CYP3A4 and P-gp increase exposure to Apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to Apixaban and increase the risk of stroke.
Strong Dual Inhibitors of CYP3A4 and P-gp: The dose of Apixaban should be decreased to 2.5mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin).
Strong Dual Inducers of CYP3A4 and P-gp: Avoid concomitant use of Apixaban Tablets with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to Apixaban.
SSRIs/SNRIs and NSAIDs: Apixaban should be used with caution when coadministered with SSRIs/SNRIs, NSAIDs, ASA and/or P2Y12 inhibitors because these medicinal products typically increase the bleeding risk.
Anticoagulants and Antiplatelet Agents: Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin and chronic NSAID use increases the risk of bleeding.

USE IN SPECIFIC POPULATIONS:
Pregnancy: There are no adequate and well-controlled studies of Apixaban Tablets in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Apixaban Tablets should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
Nursing Mothers: It is unknown whether Apixaban or its metabolites are excreted in human milk.

OVERDOSAGE: Overdose of Apixaban Tablets increases the risk of bleeding. Administration of activated charcoal may be useful in the management of Apixaban overdose or accidental ingestion by leading to a more rapid fall in Apixaban blood levels.

INSTRUCTIONS: Store below 30° C. Protect from heat, light and moisture. Keep it out of reach of children.

PRESENTATION:
Cloxipa 2.5mg Tablets are available in pack size of 30's.
Cloxipa 5mg Tablets are available in pack size of 30's.

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دُور رکھیں۔

Manufactured by:
NABIQASIM INDUSTRIES (PVT.) LTD.
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PHARMA
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