ECRU Tablets

ایکرو ٹیبلٹس

WARNING: DISCONTINUING APIXABAN IN PATIENTS WITHOUT ADEQUATE CONTINUOUS ANTICOAGULATION INCREASES RISK OF STROKE

Discontinuing Apixaban places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with Apixaban must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

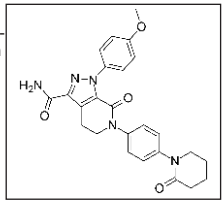
COMPOSITION

Each film coated tablet contains:

Apixaban ..... 2.5 mg & 5 mg, respectively.

DESCRIPTION

ECRU (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. Its molecular formula is C25H25N5O4, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



CLINICAL PHARMACOLOGY

Mechanism of Action: Apixaban is an oral, reversible, and selective active site inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development. **Pharmacodynamics:** As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban. **Pharmacokinetics: Absorption:** The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ECRU (Apixaban). Food does not affect the bioavailability of apixaban. Maximum concentrations (Cmax) of apixaban appear 3 to 4 hours after oral administration of ECRU (Apixaban). Apixaban is absorbed throughout the gastrointestinal tract with the distal small bowel and ascending colon contributing about 55% of apixaban absorption. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At doses ≥ 25 mg, 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 liters. **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. Following intravenous administration, apixaban is eliminated with a dominant half-life of ~ 5 hours. Following oral administration, the apparent half-life is ~12 hours because of prolonged absorption. Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

INDICATIONS

- 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 (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Active clinically significant bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor 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 haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparin s (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.

POSSIBLE ADVERSE EFFECTS

The most common and most serious adverse reactions reported with ECRU were related to bleeding.

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. 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 2.5 mg 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. In patients already taking Apixaban at a dose of 2.5 mg daily, avoid coadministration with strong dual inhibitors of both CYP3A4 and P-gp. **Strong Dual Inducers of CYP3A4 and P-gp:** Avoid concomitant use of Apixaban 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 (Clinical Pharmacology). **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including Apixaban, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from Apixaban to warfarin in clinical trials in atrial fibrillation patients. If Apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue Apixaban in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with Apixaban undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed

earlier than 24 hours after the last administration of Apixaban. The next dose of Apixaban should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of Apixaban for 48 hours. Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in Apixaban patients.

• **Prosthetic Heart Valves:** The safety and efficacy of Apixaban have not been studied in patients with prosthetic heart valves and is not recommended in these patients.

• **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of Apixaban is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

• **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including Apixaban, are not recommended for use in patients with triple-positive 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 increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

USE IN SPECIFIC POPULATIONS

Pregnancy Category B: There are no adequate and well-controlled studies of Apixaban in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Apixaban 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. Rats excrete apixaban in milk (12% of the maternal dose). Women should be instructed either to discontinue breastfeeding or to discontinue Apixaban therapy, 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:** Of the total subjects in clinical studies of apixaban, >69% were 65 and older, and >31% were 75 and older. The effects of Apixaban on the risk of stroke and major bleeding compared to warfarin were maintained in geriatric subjects.

DOSAGE AND ADMINISTRATION

• **Prevention of VTE (VTEp): elective hip or knee replacement surgery**

The recommended dose of ECRU(Apixaban) is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window. In patients undergoing hip replacement surgery: The recommended duration of treatment is 32 to 38 days. **In patients undergoing knee replacement surgery:** The recommended duration of treatment is 10 to 14 days.

• **Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF)**

The recommended dose of ECRU(Apixaban) is 5 mg taken orally twice daily.

Dose reduction: The recommended dose of ECRU(Apixaban) is 2.5 mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).

Therapy should be continued long-term.

• **Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)**

The recommended dose of ECRU(Apixaban) for the treatment of acute DVT and treatment of PE is 10 mg taken orally twice daily for the first 7 days followed by 5 mg taken orally twice daily. As per available medical guidelines, short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, immobilisation).

The recommended dose of ECRU(Apixaban) for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5 mg twice daily dose should be initiated following completion of 6 months of treatment with ECRU(Apixaban) 5 mg twice daily or with another anticoagulant.

The duration of overall therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding.

• **Missed dose**

If a dose is missed, the patient should take ECRU(Apixaban) immediately and then continue with twice daily intake as before.

• **Switching**

Switching treatment from parenteral anticoagulants to ECRU(Apixaban) (and vice versa) can be done at the next scheduled dose.

Switching from vitamin K antagonist (VKA) therapy to ECRU(Apixaban): When converting patients from vitamin K antagonist (VKA) therapy to ECRU(Apixaban), warfarin or other VKA therapy should be discontinued and ECRU(Apixaban) started when the international normalised ratio (INR) is < 2. Switching from ECRU(Apixaban) to VKA therapy: When converting patients from ECRU(Apixaban) to VKA therapy, administration of ECRU(Apixaban) should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of ECRU(Apixaban) with VKA therapy, an INR should be obtained prior to the next scheduled dose of ECRU(Apixaban). Coadministration of ECRU(Apixaban) and VKA therapy should be continued until the INR is ≥ 2. Switching between ECRU(Apixaban) and anticoagulants other than warfarin: Discontinue one being taken and begin the other at the next scheduled dose.

• **Hepatic Impairment**

No dose adjustment is required in patients with mild hepatic impairment. Apixaban is not recommended in patients with severe hepatic impairment.

• **Renal impairment**

In patients with mild or moderate renal impairment, the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), no dose adjustment is necessary.
- for the prevention of stroke and systemic embolism in patients with NVAF and serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg, a dose reduction is necessary and described above. In the absence of other criteria for dose reduction (age, body weight), no dose adjustment is necessary.

In patients with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply:

- for the prevention of VTE in elective hip or knee replacement surgery (VTEp), for the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt) apixaban is to be used with caution;
- for the prevention of stroke and systemic embolism in patients with NVAF, patients should receive the lower dose of ECRU(Apixaban) 2.5 mg twice daily. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore Apixaban is not recommended.

• **Paediatric population**

The safety and efficacy of Apixaban in children and adolescents below age 18 have not been established. No data are available.

PRECAUTIONS

Store in cool dry and dark place below 25 ^{o}C. Keep all the medicines out of reach of children. To be sold and used on the prescription of registered medical practitioners only.

PRESENTATION

ECRU(Apixaban) 2.5 mg and 5 mg Tablets are available in packing containing 30 film coated tablets, respectively.

خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: روشنی، نمی اور گرمی سے بچائیں۔ 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔ مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

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