Zilero®
(Apixaban)

زِليرو

COMPOSITION:

Each film-coated tablet contains:
Apixaban.....2.5 mg
Each film-coated tablet contains:
Apixaban.....5 mg
(As per innovator's specs.)

WARNING: (A) PREMATURE DISCONTINUATION OF APIXABAN INCREASES THE RISK OF THROMBOTIC EVENTS (B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF APIXABAN INCREASES THE RISK OF THROMBOTIC EVENTS
Premature discontinuation of any oral anticoagulant, including Apixaban, increases the risk of thrombotic events. If anticoagulation with Apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) SPINAL/EPIDURAL HEMATOMA
Epidural or spinal hematomas may occur in patients treated with APIXABAN 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. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:
• use of indwelling epidural catheters
• concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
• a history of traumatic or repeated epidural or spinal punctures
• a history of spinal deformity or spinal surgery
• optimal timing between the administration of Apixaban and neuraxial procedures is not known
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary [see Warnings and Precautions]. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

DESCRIPTION
Apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4methoxy-phenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4c]pyridine-3 carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$.

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
Apixaban displays prolonged absorption. Thus, despite a short clearance half-life of about 6 hours, the apparent half-life during repeat dosing is about 12 hours, which allows twice-daily dosing to provide effective anticoagulation, but it also means that when the drug is stopped for surgery, anticoagulation persists for at least a day.

Absorption
The absolute bioavailability of Apixaban is approximately 50% for doses up to 10 mg of Apixaban. Food does not affect the bioavailability of Apixaban. Maximum concentrations (Cmax) of Apixaban appear 3 to 4 hours after oral administration of 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
Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery Apixaban is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis
Apixaban is indicated for the treatment of DVT.
Treatment of Pulmonary Embolism
Apixaban is indicated for the treatment of PE.
Reduction in the Risk of Recurrence of DVT and PE
Apixaban is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION

Adult dosage

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation
The recommended dose of Apixaban for most patients is 5 mg taken orally twice daily.
The recommended dose of Apixaban is 2.5 mg 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 1.5 mg/dL

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery
The recommended dose of Apixaban is 2.5 mg 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 DVT and PE
The recommended dose of Apixaban is 10 mg taken orally twice daily for the first 7 days of therapy. After 7 days, the recommended dose is 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE
The recommended dose of Apixaban is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE.

Missed Dose
If a dose of Apixaban 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
Apixaban 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.
Apixaban 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 Apixaban and prior to the intervention is not generally required. Apixaban should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

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

Switching from Apixaban to warfarin:
Apixaban affects INR, so INR measurements during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue Apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of Apixaban would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching between Apixaban and anticoagulants other than warfarin:
Discontinue one being taken and begin the other at the next scheduled dose.

DOSE ADJUSTMENT IN SPECIAL POPULATIONS

Hepatic Impairment
No dose adjustment is required in patients with mild hepatic impairment. Because patients with moderate hepatic impairment may have intrinsic coagulation abnormalities and there is limited clinical experience with Apixaban in these patients, dosing recommendations cannot be provided. Apixaban is not recommended in patients with severe hepatic impairment.

Renal Impairment
Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

See DOSAGE AND ADMINISTRATION.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis.

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

CONTRAINDICATIONS
Apixaban is contraindicated in patients with the following conditions:
• Active pathological bleeding
• Severe hypersensitivity (e.g. anaphylactic reaction) to Apixaban

WARNING AND PRECAUTIONS

Increased Risk of Stroke with Discontinuation of Apixaban
Discontinuing 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 patients with nonvalvular atrial fibrillation. If Apixaban must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.

Bleeding
Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding. Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitor, and nonsteroidal anti-inflammatory drugs (NSAIDs). Patients should be made aware of signs and symptoms of blood loss and instructed to report them immediately or go to an emergency room. Apixaban should be discontinued in patients with active pathological hemorrhage.
There is no established way to reverse the anticoagulant effect of Apixaban, which can be expected to persist for about 24 hours after the last dose, i.e., for about two half-lives. A specific antidote for Apixaban is not available. Because of high plasma protein binding, Apixaban is not expected to be dialyzable. Protamine sulfate and vitamin K would not be expected to affect the anticoagulant activity of Apixaban. There is no experience with antifibrinolytic agents (Tranexamic acid, Aminocaproic acid) in individuals receiving Apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (Desmopressin and Aprotinin) in individuals receiving Apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of Apixaban, thereby lowering Apixaban plasma concentration.
Avoid use in elderly patients with CrCl less than 25 mL/min due to increased risk of bleeding

Patients with Prosthetic Heart Valves
The safety and efficacy of Apixaban has not been studied in patients with prosthetic heart valves. Therefore, use of Apixaban is not recommended in these patients.

ADVERSE REACTIONS
The following serious adverse reactions may occur with Apixaban:
• Increased risk of thrombotic events after premature discontinuation
• Bleeding
• Spinal/epidural anesthesia or puncture
* There were no occurrences of generalized pruritus in CV185057 (long term prevention of VTE)

System Organ Class	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
Blood and lymphatic system disorders		
Anaemia	Common	Common
Thrombocytopenia	Uncommon	common
Immune system disorders		
Hypersensitivity, allergic oedema and Anaphylaxis	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon
Nervous system disorders		
Brain haemorrhage†	Uncommon	Rare
Eye disorders		
Eye haemorrhage (including conjunctival haemorrhage)	Common	Uncommon
Vascular disorders		
Haemorrhage, haematoma	Common	Common
Hypotension (including procedural hypotension)	Common	Uncommon
Intra-abdominal haemorrhage	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common	Common
Haemoptysis	Uncommon	Uncommon
Respiratory tract haemorrhage	Rare	Rare
Gastrointestinal disorders		
Nausea	Common	Common
Gastrointestinal haemorrhage	Common	Common
Haemorrhoidal haemorrhage	Uncommon	Uncommon
Mouth haemorrhage	Uncommon	Common
Haematochezia	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Common	Common
Retroperitoneal haemorrhage	Rare	Not known
Hepatobiliary disorders		
Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Common	Common
Alanine aminotransferase increased	Uncommon	Common
Skin and subcutaneous tissue disorders		
Skin rash	Uncommon	Common
Musculoskeletal and connective tissue disorders		
Muscle haemorrhage	Rare	Uncommon
Renal and urinary disorders		
Haematuria	Common	Common
Reproductive system and breast disorders		
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Common
General disorders and administration site conditions		
Application site bleeding	Uncommon	Uncommon
Investigations		
Occult blood positive	Uncommon	Uncommon
Injury, poisoning and procedural complications		
Contusion	Common	Common
Post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage	Uncommon	Uncommon
Traumatic haemorrhage	Uncommon	Uncommon

† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (ie., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

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 and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors
For patients receiving Apixaban 5 mg or 10 mg twice daily, the dose of Apixaban should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir). For patients receiving Apixaban at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors.
Clarithromycin
Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with Apixaban

Combined P-gp and Strong CYP3A4 Inducers
Avoid concomitant use of Apixaban with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to Apixaban.

Anticoagulants and Antiplatelet Agents
Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

USE IN SPECIAL POPULATIONS

Pregnancy
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 mother
It is unknown whether Apixaban or its metabolites are excreted in human milk. Women should be instructed either to discontinue breastfeeding or to discontinue Apixaban therapy, taking into account the importance of the drug to the mother.

Pediatrics
Safety and effectiveness in pediatric patients have not been established.

Elderly
No clinically significant differences in safety or effectiveness are observed when comparing subjects in different age groups.

Renal impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation
The recommended dose is 2.5 mg 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 1.5 mg/dL

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE.
No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with Apixaban in these patients, dosing recommendations cannot be provided. Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh class C).

OVER DOSAGE
Overdose of Apixaban increases the risk of bleeding. A toxic dose has not been established. Administration of activated charcoal may be useful in the management of recent Apixaban overdose or accidental ingestion. An antidote (i.e., coagulation factor Xa) may be indicated in patients that require reversal of anticoagulation following a clinically significant Apixaban exposure.

PRESENTATION
Zilero 2.5mg: Pack of 30 Tablets
Zilero 5mg: Pack of 30 Tablets

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, report at reports@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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