Apiban®

(Apixaban)

Highnoon

COMPOSITION
Apiban 2.5mg Tablet: Each film-coated tablet contains:
Apixaban 2.5mg
Apiban 5mg Tablet: Each film-coated tablet contains:
Apixaban 5mg

DESCRIPTION
Apiban contains Apixaban which is a factor Xa (FXa) inhibitor.

Mechanism of Action
Apixaban is a selective 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.

PHARMACOKINETICS
Apixaban is rapidly absorbed with an absolute bioavailability of about 50% and peak plasma concentrations occurring 3 to 4 hours after an oral dose. Apixaban is metabolized in the liver mainly via P450 cytochromes CYP3A4 and CYP3A5. It is excreted renally and in the faeces as unchanged drug and inactive metabolites. The half life is about 12 hours. Apixaban is a substrate of the transport protein P-glycoprotein.

INDICATIONS AND USAGE
It is indicated in the following conditions:
- Reduces the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
- Prophylaxis of venous thromboembolism following knee and hip replacement surgery.
- Treatment of deep vein thrombosis (DVT).
- Treatment of pulmonary embolism (PE).
- Reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION
Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation
- The recommended dose of Apixaban for most patients is 5mg 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:
  - o age greater than or equal to 80 years
  - o body weight less than 61 kg
  - o serum creatinine greater than or equal to 1.5 mg/dL (133 micromole / litre)

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.
  - o In patients undergoing hip replacement surgery, the recommended duration of treatment is 32-38 days.
  - o In patients undergoing knee replacement surgery, the recommended duration of treatment is 10-14 days.

Treatment of DVT and PE
- The recommended dose 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.

If a dose 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.

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

WARNINGS AND PRECAUTIONS
- Premature discontinuation of any oral anticoagulant, including Apixaban, or 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. If Apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

- 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 inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Advise patients of signs and symptoms of blood loss to report them immediately or go to an emergency room. Discontinue Apixaban in patients with active pathological hemorrhage.

- The pharmacodynamic effect of Apixaban can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be may be considered when requiring reversal of Apixaban effects. When PCCs are used, monitoring for the anticoagulation effect of Apixaban using a clotting test (PT, INR, or APTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering Apixaban plasma concentration. Hemodialysis does not appear to have a substantial impact on Apixaban exposure. Protamine sulfate and vitamin K are not 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 no experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban, and they are not expected to be effective as a reversal agent.

- When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic 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. 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 for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

- The safety and efficacy of Apixaban have not been studied in patients with prosthetic heart valves. Therefore, use of Apixaban is not recommended in these patients.

- 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.

- 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 its location and easily controlled. Bridging anticoagulation during the 24 hours 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.

- Direct-acting oral anticoagulants (DOACs), including apixaban, are not recommended for use in patients with triple-positive antiphospholipid syndrome (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.

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

ADVERSE REACTIONS
The serious reported adverse events of Apixaban are: increased risk of thrombotic events after premature discontinuation, bleeding, spinal/epidural anesthesia or puncture, decrease in hemoglobin, intracranial bleed includes (intracerebral, intraventricular, subdural, and subarachnoid bleeding), major bleeding at critical sites (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome), hemorrhagic stroke, GI bleeding includes (upper GI, lower GI, and rectal bleeding) and fatal bleeding leads to death. The other reported adverse events are hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema), syncope, nausea, anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters), contusion, hemorrhage (including hematoma, and vaginal and urethral hemorrhage), postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma, and catheter-site hemorrhage), transaminases increase (including aminotransferase increase and abnormal alanine aminotransferase), aspartate aminotransferase increase, gamma-glutamyl transferase increase, thrombocytopenia (including platelet count decrease), hypotension (including procedural hypotension), epistaxis, gastrointestinal hemorrhage (including hematemesis and melena), hematochezia, abnormal liver function test, blood alkaline phosphatase increase, blood bilirubin increase, hematuria, wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage, gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage, hematoma and menorrhagia. The less commonly reported adverse events are: hemorrhagic anemia, hemorrhoidal hemorrhage, anal hemorrhage, traumatic hematoma, periorbital hematoma, vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage, vascular hemorrhage, ecchymosis, skin hemorrhage, petechiae, conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage, blood urine present, occult blood positive, occult blood, red blood cells urine positive, injection-site hematoma and vessel puncture-site hematoma.

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 Inhibitor**
  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 SPECIFIC POPULATIONS
Pregnancy
The limited available data on Apixaban use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Labor and Delivery
All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. Apixaban use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

Nursing Mothers
It is unknown whether Apixaban or its metabolites are excreted in human milk, the effects on the breastfed child, or the effects on milk production. Breastfeeding is not recommended during Apixaban treatment.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Use of anticoagulants, including apixaban, may increase the risk of bleeding in the fetus and neonate.

Geriatric Use
No clinically significant differences in safety or effectiveness were 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
- o age greater than or equal to 80 years
- o body weight less than 61 kg
- o serum creatinine greater than or equal to 1.5 mg/dL (133 micromole/L)

Patients with End-Stage Renal Disease on Dialysis
Clinical efficacy and safety studies with Apixaban with end-stage renal disease (ESRD) on dialysis have not been studied.
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).

OVERDOSAGE
Overdose of Apixaban increases the risk of bleeding. Administration of activated charcoal may be useful in the management of Apixaban overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of Apixaban is available.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Apiban 2.5mg Tablets: Alu. Alu. Blister Pack of 3 x 10's.
Apiban 5mg Tablets: Alu. Alu. Blister Pack of 3 x 10's.

اپِبین®

(ایپکسابین)

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔

بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔

خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14002927