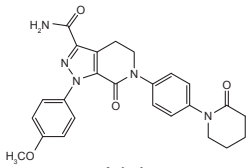
Apixaget™

[A p i x a b a n]

اپیکزاگیٹ

Tablets 2.5mg & 5mg

DESCRIPTION
Apixaget (Apixaban) is a direct inhibitor of activated factor X (factor Xa). Chemically, it is 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$ and the structural formula is:



Apixaban

QUALITATIVE AND QUANTITATIVE COMPOSITION
Apixaget (Apixaban) Tablets are available for oral administration as:

Apixaget Tablets 2.5mg
Each film-coated tablet contains:
Apixaban…2.5mg

Apixaget Tablets 5mg
Each film-coated tablet contains:
Apixaban…5mg

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.

Pharmacokinetic
Absorption
The absolute bioavailability of Apixaban is approximately 50% for doses upto 10mg. Apixaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 3 to 4 hours after tablet intake. Intake with food does not affect Apixaban AUC or C_{max} at the 10mg dose. At doses ≥ 25mg Apixaban displays dissolution-limited absorption with decreased bioavailability.

Distribution
Average plasma protein binding in humans is approximately 87% to 93%. The volume of distribution (V_{ss}) is approximately 21 liters.

Metabolism
Approximately 25% of an orally administered Apixaban dose is recovered in urine and feces as metabolites. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolized mainly via CYP 3A4/5 with minor contributions from CYP 1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged Apixaban is the major drug-related component in human plasma with no active circulating metabolites being present. Apixaban is a substrate of transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Excretion
Apixaban has multiple routes of elimination. Approximately 25% was recovered from the administered Apixaban dose in humans, as metabolites, with the majority recovered in feces. Renal excretion of Apixaban accounts for approximately 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of Apixaban in the feces. Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

THERAPEUTIC INDICATIONS
Apixaget (Apixaban) is indicated for:
- The prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective knee or hip replacement surgery.
- The prevention of stroke and systemic embolism in patients with atrial fibrillation.
- The treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.

DOSAGE & ADMINISTRATION
Prevention of stroke and systemic embolism in patients with atrial fibrillation
The recommended dose of Apixaget (Apixaban) for most patients is 5mg taken orally twice daily. The recommended dose of Apixaget (Apixaban) 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

Prevention of venous thromboembolic events (VTE) following Hip or Knee Replacement Surgery
The recommended dose of Apixaget (Apixaban) 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 32 - 38 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 10 - 14 days.

Treatment of DVT and PE and Prevention of recurrent DVT and PE
The recommended dose of Apixaget (Apixaban) is 10mg taken orally twice daily for 7 days, followed by 5mg taken orally twice daily for the treatment of acute DVT or PE.
The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk of bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and extended duration should be based on permanent risk factors or idiopathic DVT or PE.

Further to the course of a minimum of 6 months of treatment for DVT or PE, the recommended dose for the continued prevention of recurrent DVT and PE is 2.5mg taken orally twice daily.

Method of administration
Apixaget (Apixaban) Tablets should be administered with water, with or without food.
For patients who are unable to swallow whole tablets, Apixaget (Apixaban) Tablets may be crushed and suspended in water or 5% dextrose in water (D5W), or apple juice or mixed with applesauce and immediately administered orally. Alternatively, Apixaget (Apixaban) Tablets may be crushed and suspended in 60mL of water or D5W and immediately delivered through a nasogastric tube. Crushed Apixaget (Apixaban) Tablets are stable in water, D5W, apple juice, and applesauce for upto 4 hours.

Missed dose
If a dose is missed, the patient should take Apixaget (Apixaban) immediately and then continue with twice daily intake as before. The dose should not be doubled to make up for a missed dose.

Temporary Interruption for Surgery and Other Interventions
Apixaget (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. Apixaget (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 Apixaget (Apixaban) and prior to the intervention is not generally required. Apixaget (Apixaban) should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Switching
Switching treatment from parenteral anticoagulants to Apixaget (Apixaban) Tablets (and vice versa) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously.

Switching from vitamin K antagonist (VKA) therapy to Apixaget (Apixaban)
When converting patients from vitamin K antagonist (VKA) therapy to Apixaget (Apixaban), warfarin or other VKA therapy should be discontinued and Apixaget (Apixaban) started when the international normalised ratio (INR) is < 2.

Switching from Apixaget (Apixaban) to vitamin K antagonist (VKA) therapy
When converting patients from Apixaget (Apixaban) to VKA therapy, administration of Apixaget (Apixaban) should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Apixaget (Apixaban) with VKA therapy, an INR should be obtained prior to the next scheduled dose of Apixaget (Apixaban). Coadministration of Apixaget (Apixaban) and VKA therapy should be continued until the INR is ≥ 2.

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

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

Combined P-gp and Strong CYP3A4 Inhibitors
For patients receiving Apixaget (Apixaban) doses of 5mg or 10mg twice daily, reduce the dose by 50% when Apixaget (Apixaban) is co-administered with drugs that are combined P-glycoprotein (P-gp) and strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, itraconazole, ritonavir). In patients already taking 2.5mg twice daily, avoid co-administration of Apixaget (Apixaban) with combined P-gp and strong CYP3A4 inhibitors.

Special Population
Renal Impairment
Prevention of VTE following Elective Hip or Knee Replacement Surgery and Treatment of DVT and PE and Prevention of recurrent DVT and PE:
In patients with severe renal impairment (creatinine clearance 15-29 mL/min), Apixaget (Apixaban) is to be used with caution in these patients because of potentially higher bleeding risk.

Hemodialysis in ESRD Patients:
Systemic exposure to Apixaget (Apixaban) administered as a single 5mg dose in ESRD patients dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to patients with normal renal function.
The systemic exposure to Apixaget (Apixaban) administered 2 hours prior to a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min is 17% higher compared to those with normal renal function. The dialysis clearance of Apixaget (Apixaban) is approximately 18 mL/min. The systemic exposure of Apixaget (Apixaban) is 14% lower on dialysis when compared to not on dialysis. Protein binding was similar (92% - 94%) between healthy controls and ESRD subjects during the on-dialysis and off-dialysis periods.

Hepatic Impairment
It is not recommended in patients with severe hepatic impairment. It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment.

Cardioversion
Patients can stay on Apixaget (Apixaban) while being cardioverted.

Paediatric population
The safety and efficacy of Apixaget (Apixaban) in children and adolescents below age 18 have not been established.

ADVERSE REACTIONS
Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery

Common:
Anaemia, haemorrhage, haematoma, nausea and contusion.

Uncommon:
Thrombocytopenia, pruritus, hypotension (including procedural hypotension), epistaxis, gastrointestinal haemorrhage, haematochezia, transaminases increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased, haematuria, 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) and operative haemorrhage.

Rare:
Hypersensitivity, allergic oedema, anaphylaxis, eye haemorrhage (including conjunctival haemorrhage), haemoptysis, rectal haemorrhage, gingival bleeding and muscle haemorrhage.

Prevention of stroke and systemic embolism in adult patients with Non Valvular Atrial Fibrillation, with one or more risk factors (Non Valvular Atrial Fibrillation)

Common:
Eye haemorrhage (including conjunctival haemorrhage), haemorrhage, haematoma, epistaxis, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, haematuria and contusion.

Uncommon:
Hypersensitivity, allergic oedema and anaphylaxis, pruritus, brain haemorrhage, intra-abdominal haemorrhage, haemoptysis, haemorrhoidal haemorrhage, mouth haemorrhage, haematochezia, skin rash, abnormal vaginal haemorrhage, urogenital haemorrhage, application site bleeding, occult blood positive, traumatic haemorrhage, post procedural haemorrhage and incision site haemorrhage.

Rare:
Respiratory tract haemorrhage, retroperitoneal haemorrhage and muscle haemorrhage.

Treatment of DVT and PE, and prevention of recurrent DVT and PE

Common:
Haemorrhage, haematoma, epistaxis, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, haematuria and contusion.

Uncommon:
Pruritus, eye haemorrhage (including conjunctival haemorrhage), haemoptysis, haematochezia, abnormal vaginal haemorrhage, urogenital haemorrhage, occult blood positive, traumatic haemorrhage, post procedural haemorrhage and incision site haemorrhage.

Rare:
Brain haemorrhage and respiratory tract haemorrhage.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Apixaban is contraindicated in:
- Hypersensitivity to the active substance or to any of the excipient of the product.
- Active clinically significant bleeding including GI bleeding.
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- Lesion or condition if considered a significant risk factor for major bleeding e.g., 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 systemic treatment with HIV protease inhibitors, e.g., ritonavir.
- Concomitant treatment with any other anticoagulant, including
  - Unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
  - Low molecular weight heparins (LMWH), such as enoxaparin and dalteparin,
  - Heparin derivatives, such as fondaparinux, and
  - Oral anticoagulants, such as warfarin, dabigatran, rivaroxaban, except under circumstances of switching therapy to or from Apixaban.

PRECAUTION

WARNING
Premature Discontinuation of Apixaban increases the Risk of Thrombotic Events:
Premature discontinuation of any oral anticoagulant, including Apixaban, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if Apixaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

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.
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

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 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
Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding. 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.

Spinal/Epidural Anesthesia or Puncture
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. Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated. Patients at high risk of bleeding should not be prescribed Apixaban.

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.

Patients with Prosthetic Heart Valves
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.

Patients with antiphospholipid syndrome
Direct acting Oral Anticoagulants (DOACs) including Apixaban are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Temporary discontinuation
Discontinuing anticoagulants, including Apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided and if anticoagulation with Apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

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 Mothers
It is unknown whether Apixaban or its metabolites are excreted in human milk. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from Apixaban therapy.

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 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, platelet aggregation inhibitors and NSAIDs
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated. Medicinal products associated with serious bleeding are not recommended concomitantly with Apixaban such as: thrombolytic agents, fibrinolytics, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran, heparin, aspirin, chronic NSAID and sulfinpyrazone.

OVERDOSAGE:
There is no antidote to Apixaban. Overdose of Apixaban may result in a higher risk of bleeding. In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered.
Administration of activated charcoal 2 and 6 hours after ingestion of a 20mg dose of Apixaban reduced mean Apixaban AUC by 50% and 27%, respectively, and had no impact on C_{max}. Mean half-life of Apixaban decreased from 13.4 hours when Apixaban was administered alone to 5.3 hours and 4.9 hours, respectively, when activated charcoal was administered 2 and 6 hours after Apixaban. Thus, administration of activated charcoal may be useful in the management of Apixaban overdose or accidental ingestion.
Haemodialysis decreased Apixaban AUC by 14% in subjects with end-stage renal disease (ESRD), when a single dose of Apixaban 5mg was administered orally. Therefore, haemodialysis is unlikely to be an effective means of managing Apixaban overdose.
If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:
- activated prothrombin complex concentrate (APCC), e.g., FEIBA
- prothrombin complex concentrate (PCC)
- recombinant Factor-VIIa (rFVIIa)

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED
Apixaget (Apixaban) Tablets 2.5mg are available in blister pack of 30's.
Apixaget (Apixaban) Tablets 5mg are available in blister pack of 30'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.

Manufactured by:

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L-200012633