02-09-0446

APXAN

(Apixaban Tablets)

Product Specifications: Innovator
Apxan Tablets 2.5 mg: Each film coated tablets contains: Apixaban ..... 2.5 mg
Product contains Lactose
Apxan Tablets 5 mg: Each film coated tablets contains: Apixaban ..... 5 mg
Product contains Lactose

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. 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.

SPINAL/EPIDURAL HEMATOMA

Epiral or spinal hematomas may occur in individuals 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 individuals for spinal procedures. Factors that can increase the risk 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
- History of traumatic or repeated epidural or spinal punctures
- History of spinal deformity or spinal surgery
- Optimal timing between the administration of apixaban and neuraxial procedures is not known

Monitor individuals 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.

DESCRIPTION

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-tetrahydro1H-pyrazolo[3,4-c]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5.

PHARMACEUTICAL FORM: Film Coated Tablets

CLINICAL PARTICULARS

Therapeutic indications

Apxan (apixaban) is indicated for:

- The Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- The 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).
- The Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Posology and method of administration

Prevention of venous thromboembolic events (VTEp): elective 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 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 apixaban is 5 mg taken orally twice daily.
- The recommended dose of 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 and PE and prevention of recurrent DVT and PE (VTEt):

- The recommended dose of 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, immobilization).
- The recommended dose of 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 apixaban 5 mg twice daily.
- 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 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: Apxan (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. Apxan (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 Apxan (apixaban) and prior to the intervention is not generally required. Apxan (apixaban) should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

Converting from or to Apxan (apixaban)

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

Switching from Apxan (apixaban) to warfarin:

Apxan (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 Apxan (apixaban) and begin both a parenteral anticoagulant and warfarin at the time the next dose of Apxan (apixaban) would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching from Apxan (apixaban) to anticoagulants other than warfarin (oral or parenteral):

Discontinue Apxan (apixaban) and begin taking the new anticoagulant other than warfarin at the usual time of the next dose of Apxan (apixaban).

Switching from anticoagulants other than warfarin (oral or parenteral) to Apxan (apixaban):

Discontinue the anticoagulant other than warfarin and begin taking Apxan (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 Apxan (apixaban) doses of 5 mg or 10 mg twice daily, reduce the dose by 50% when coadministered 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 2.5 mg twice daily, avoid coadministration of Apxan (apixaban) with combined P-gp and strong CYP3A4 inhibitors.

Special population

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, the recommended dose is 2.5 mg taken orally twice daily. 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 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.

Hepatic impairment

- Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
- It is not recommended in patients with severe hepatic impairment (child-pugh class C)
- 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
- Patients with elevated liver enzymes alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore, apixaban should be used with caution in this population. Prior to initiating apixaban, liver function testing should be performed.

Patients undergoing catheter ablation (NVAF)

Patients can continue apixaban use while undergoing catheter ablation.

Patients undergoing cardioversion

Apixaban can be initiated or continued in NVAF patients who may require cardioversion.

- For patients not previously treated with anticoagulants, exclusion of left atrial thrombus using an image guided approach (e.g. transesophageal echocardiography (TEE) or computed tomographic scan (CT)) prior to cardioversion should be considered, in accordance with established medical guidelines.
- For patients initiating treatment with apixaban, 5 mg should be given twice daily for at least 2.5 days (5 single doses) before cardioversion to ensure adequate anticoagulation. The dosing regimen should be reduced to 2.5 mg apixaban given twice daily for at least 2.5 days (5 single doses) if the patient meets the criteria for dose reduction.
- If cardioversion is required before 5 doses of apixaban can be administered, a 10 mg loading dose should be given, followed by 5 mg twice daily. The dosing regimen should be reduced to a 5 mg loading dose followed by 2.5 mg twice daily if the patient meets the criteria for dose reduction. The administration of the loading dose should be given at least 2 hours before cardioversion.
- For all patients undergoing cardioversion, confirmation should be sought prior to cardioversion that the patient has taken apixaban as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with NVAF and acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI)

There is limited experience of treatment with apixaban at the recommended dose for NVAF patients when used in combination with antiplatelet agents in patients with ACS and/or undergoing PCI after haemostasis is achieved.

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

Method of Administration: Apxan (apixaban) is for Oral use. Apixaban should be swallowed with water, with or without food. For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg Apxan (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, Apxan (apixaban) tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube.
Crushed Apxan (apixaban) tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours.

Contraindication

- Hypersensitivity to the active substance or to any of the excipients of the product.
- 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 heparins (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.

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. 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. 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.) Discontinue apixaban in patients with active pathological hemorrhage.

Spinal/Epidural Anesthesia or Puncture: When neuraxial anaesthesia (spinal/epidural anaesthesia) 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 haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of apixaban. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment. 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.
There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case there is such need and based on the general PK characteristics of apixaban, a time interval of 20-30 hours (i.e., 2 x half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter removal. As with all new anticoagulant medicinal products, experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

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.

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: 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.

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.

Patients with active cancer: Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events. When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made.

Elderly patients: Increasing age may increase haemorrhagic risk. Also, the coadministration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk.

Hip fracture surgery: Apixaban has not been studied in clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, it is not recommended in these patients.

Information about excipients: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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**.** In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk: 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.

Fetal/Neonatal adverse reactions: Use of anticoagulants, including apixaban, may increase the risk of bleeding in the fetus and neonate.

Labor or 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.

Breast-feeding: Apixaban and/or its metabolites were present in the milk of rats. Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with apixaban.

Females and Males of Reproductive Potential: Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including apixaban should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

Geriatric Use: No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

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.
- Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (eg. amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil,) are expected to increase apixaban plasma concentration to a lesser extent. No dose adjustment for apixaban is required when co-administered with them.
- 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: 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, antiplatelet, fibrinolytics, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran, heparin, aspirin, chronic NSAID and sulfinpyrazone.
- Other concomitant therapies: No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was coadministered with atenolol or famotidine.
- Effect of apixaban on other medicinal products: In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 µM) and weak inhibitory effect on the activity of CYP2C19 (IC50 > 20 µM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6 and CYP3A4/5 at a concentration up to 20 µM. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered medicinal products that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp.
- In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Carcinogenesis, Mutagenesis, impairment of fertility

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and embryo-fetal development and juvenile toxicity.

Adverse Reactions

Tabulated list of adverse reactions Table 2 shows the adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively.

Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)

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

Uncommon: Thrombocytopenia, pruritus, hypotension (including procedural hypotension), epistaxis, gastrointestinal haemorrhage, haematochezia, Alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased, haematuria, abnormal vaginal haemorrhage, urogenital haemorrhage, 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, alopecia 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: Anemia, eye haemorrhage (including conjunctival haemorrhage), haemorrhage, haematoma, Hypotension (including procedural hypotension), epistaxis, nausea, Gamma- glutamyltransferase increased, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, haematuria and contusion.

Uncommon: Thrombocytopenia, hypersensitivity, allergic oedema and anaphylaxis, pruritus, brain haemorrhage, intra-abdominal haemorrhage, haemoptysis, haemorrhoidal haemorrhage, mouth haemorrhage, haematochezia, Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, Alanine aminotransferase increased, alopecia, skin rash, abnormal vaginal haemorrhage, urogenital haemorrhage, application site bleeding, occult blood positive, traumatic haemorrhage, 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: Respiratory tract haemorrhage, retroperitoneal haemorrhage and muscle haemorrhage.

Very rare: Erythema multiforme

Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)

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

Uncommon: Pruritus, eye haemorrhage (including conjunctival haemorrhage), periorbital hematoma, haemoptysis, haematochezia, abnormal vaginal haemorrhage, metrorrhagia, menometrorrhagia, urogenital haemorrhage, occult blood positive, traumatic haemorrhage, skin hemorrhage, ecchymosis, post procedural haemorrhage and incision site haemorrhage.

Rare: Brain haemorrhage and respiratory tract haemorrhage.

Effect on ability to drive and use machines

Apixaban has no or negligible influence on the ability to drive and use machines.

Overdosage

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, the transfusion of fresh frozen plasma or the administration of a reversal agent for factor Xa inhibitors should be considered.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20 mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively, and had no impact on Cmax. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

Reversal of Anticoagulant Effect: An agent to reverse the anti-factor Xa activity of apixaban is available. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Effect of PCCs on Pharmacodynamics of apixaban**:** There is no clinical experience to reverse bleeding with the use of 4-factor PCC products in individuals who have received apixaban. Effects of 4-factor PCCs on the pharmacodynamics of apixaban were studied in healthy subjects. Following administration of apixaban dosed to steady state, endogenous thrombin potential (ETP) returned to pre-apixaban levels 4 hours after the initiation of a 30-minute PCC infusion, compared to 45 hours with placebo. Mean ETP levels continued to increase and exceeded pre-apixaban levels reaching a maximum (34%-51% increase over pre-apixaban levels) at 21 hours after initiating PCC and remained elevated (21%-27% increase) at the end of the study (69 hours after initiation of PCC). The clinical relevance of this increase in ETP is unknown.

Cardiac Electrophysiology: Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

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 demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

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. 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. Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration. Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Hemodialysis in ESRD subjects: Systemic exposure to apixaban administered as a single 5 mg dose in ESRD subjects dosed immediately after the completion of a 4-hour hemodialysis session (post-dialysis) is 36% higher when compared to subjects with normal renal function. The systemic exposure to 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 apixaban is approximately 18 mL/min. The systemic exposure of 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.

HOW SUPPLIED

Apxan Tablet 2.5 mg: Pack of 30 Tablets
Apxan Tablet 5 mg: Pack of 30 Tablets

STORAGE

Do not store above 30°C.
The expiration date refers to the product correctly stored at the required condition.

INSTRUCTIONS

Keep away from heat, light and moisture. Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.

Please read the contents cautiously before use.
This package insert is regularly and timely updated.

Manufactured by:

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