30-07-2021
1st Copy

210mm

AFIXBA™ Tablet
(A p i x a b a n)

WARNING: DISCONTINUING AFIXBA™ 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 apixaban in clinical trials in patients with non valvular atrial fibrillation. If anticoagulation with apixaban must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

QUALITATIVE AND QUANTITATIVE COMPOSITION

AFIXBA™ Tablet 2.5mg
Each film coated tablet contains:
Apixaban MS..... 2.5mg

AFIXBA™ Tablet 5mg
Each film coated tablet contains:
Apixaban MS..... 5mg

PHARMACEUTICAL FORM
Tablet

CLINICAL PARTICULARS
THERAPEUTIC INDICATIONS:
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.

POSOLOGY AND METHOD OF ADMINISTRATION
Posology:
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF): The recommended dose of apixaban is 5mg taken orally twice daily.
Dose reduction: The recommended dose of apixaban is 2.5mg taken orally twice daily in patients with NVAF and at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg, or serum creatinine ≥ 1.5mg/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 apixaban for the treatment of acute DVT and treatment of PE is 10mg taken orally twice daily for the first 7 days followed by 5mg taken orally twice daily. Short duration of treatment (at least 3 months) should be based on transient risk factors (e.g., recent surgery, trauma, and immobilisation).
The recommended dose of apixaban for the prevention of recurrent DVT and PE is 2.5mg taken orally twice daily. When prevention of recurrent DVT and PE is indicated, the 2.5mg twice daily dose should be initiated following completion of 6 months of treatment with apixaban 5mg twice daily or with another anticoagulant.

Dose Recommendation (VTEt)

	Dosing schedule	Maximum daily dose
Treatment of DVT or PE	10mg twice daily for the first 7 days	20mg
	followed by 5mg twice daily	10mg
Prevention of recurrent DVT and/or PE following completion of 6 months of treatment for DVT or PE	2.5mg twice daily	5mg

The duration of overall therapy should be individualized 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.
Switching: Switching treatment from parenteral anticoagulants to AFIXBA™ (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 Apixaban: When converting patients from vitamin K antagonist (VKA) therapy to apixaban, warfarin or other VKA therapy should be discontinued and apixaban started when the international normalised ratio (INR) is < 2.
Switching from Apixaban to VKA therapy: When converting patients from apixaban to VKA therapy, administration of apixaban should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of apixaban with VKA therapy, an INR should be obtained prior to the next scheduled dose of apixaban.
Coadministration of apixaban and VKA therapy should be continued until the INR is ≥ 2.
Elderly: ***In VTEt and NVAF:*** No dose adjustment required unless criteria for dose reduction are met.
Renal impairment: In patients with mild or moderate renal impairment, the following recommendations apply:
- 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 ≥1.5mg/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 patient with severe renal impairment (creatinine clearance 15-29 mL/min) the following recommendations apply:
- 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 2.5mg 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.
Gender and Body weight: In Both VTEt & NVAF No dose adjustment required.
Patients undergoing catheter ablation (NVAF): Patients can continue while undergoing catheter ablation.
Patients undergoing cardioversion: For patients initiating treatment with apixaban, 5mg 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 2.5mg 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 10mg loading dose should be given, followed by 5mg twice daily. The dosing regimen should be reduced to a 5mg loading dose followed by 2.5mg 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.
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: Safety and efficacy below 18 years have not been established. No data are available.
Method of administration: Oral use. Apaxiban should be swallowed with water, with or without food.

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 esophageal 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Haemorrhage risk: Patients taking apixaban are to be carefully observe for signs of bleeding. Apixaban should be discontinued if severe haemorrhage occurs.
Interaction with other medicinal products affecting haemostasis: Concomitant treatment with any other anticoagulants is contraindicated. Care is to be taken if patients are treated concomitantly with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), or non-steroidal anti-inflammatory medicinal products (NSAIDs), including acetylsalicylic acid. In patients with atrial fibrillation a careful assessment should be made before combining this therapy with apixaban.
Use of thrombolytic agents for the treatment of acute ischemic stroke: Very limited experience available.
Patients with prosthetic heart valves: Use of apixaban is not recommended in this setting.
Patients with antiphospholipid syndrome: Not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome.
Surgery and invasive procedures: Apixaban should be discontinue at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted.
Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy: Apixaban is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy.

120mm

30-07-2021
1st Copy

210mm

Patients with active cancer: When apixaban is considered for DVT or PE treatment in cancer patients, a careful assessment of the benefits against the risks should be made.
Patients with renal impairment: Limited clinical data indicate that apixaban plasma concentrations are increased in patients with severe renal impairment (creatinine clearance 15-29 mL/min) which may lead to an increased bleeding risk. In patients with creatinine clearance < 15 mL/min, or in patients undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.
Elderly patients: Co-administration of apixaban with ASA in elderly patients should be used cautiously because of a potentially higher bleeding risk. Low body weight (< 60kg) may increase haemorrhagic risk.
Patients with 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).
Interaction with inhibitors of both cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp): The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV protease inhibitors (e.g., ritonavir).
Laboratory parameters: Clotting tests [e.g., prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT)] are affected as expected by the mechanism of action of apixaban.
Information about excipients: Apixaban contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicinal product. This medicinal product contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially "sodium-free".

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
Inhibitors of CYP3A4 and P-gp: The use of apixaban is not recommended such as azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole) and HIV Protease inhibitors (e.g., ritonavir). Other drugs such as amiodarone, clarithromycin, diltiazem, fluconazole, naproxen, quinidine, verapamil are expected to increase apixaban plasma concentration to a lesser extent.
Inducers of CYP3A4 and P-gp: Concomitant use of apixaban with other strong inducers like, phenytoin, carbamazepine, phenobarbital or St. John's Wort may also lead to reduced apixaban plasma concentrations.
Anticoagulants, platelet aggregation inhibitors, SSRIs/SNRIs and NSAIDs: Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated except under specific circumstances of switching anticoagulant therapy.
Other concomitant therapies: No clinically significant pharmacokinetic or pharmacodynamics interactions were observed when apixaban was co administered with atenolol or famotidine.
Effect of apixaban on other medicinal products:
Digoxin: Co administration of apixaban (20mg once a day) and digoxin (0.25mg once a day), did not affect digoxin AUC or Cmax.
Naproxen: Co administration of single doses of apixaban (10mg) and naproxen (500mg) did not have any effect on the naproxen AUC or Cmax.
Atenolol: Co administration of a single dose of apixaban (10mg) and atenolol (100mg) did not alter the pharmacokinetics of atenolol.
Activated charcoal: Administration of activated charcoal reduces apixaban exposure.

FERTILITY, PREGNANCY AND LACTATION:
Fertility: Studies in animals dosed with apixaban have shown no effect on fertility.
Pregnancy: No data available. It is preferable to avoid the use of apixaban during pregnancy.
Lactation: Discontinue breast-feeding or to discontinue/abstain from apixaban therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: No or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS:
Common adverse reactions found in clinical trials were haemorrhage, contusion, epistaxis, and haematoma.
Adverse events in prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF) and treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt).
Common: Blood and lymphatic system disorder: Anaemia, Haemorrhage, haematoma, epistaxis, nausea, gastrointestinal haemorrhage, rectal haemorrhage, gingival bleeding, gamma glutamyl transferase increased, hematuria, contusion.
Uncommon to Rare: Thrombocytopenia, hypersensitivity, allergic edema and anaphylaxis, pruritus, liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, hematochezia, alopecia, 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), operative haemorrhage, brain and eye haemorrhage, abnormal vaginal/ urogenital haemorrhage intra-abdominal haemorrhage, respiratory tract haemorrhage, skin and mouth haemorrhage, alaninie aminotransferase increased, muscle haemorrhage.

The use of apixaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in post haemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding.

OVERDOSE:
Overdose may result in a higher risk of bleeding. 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. Administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES:
Therapeutic Classification: Antithrombotic agents, direct factor Xa inhibitors. **ATC code:** B01AF02
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. 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 PROPERTIES:
Absorption: Apixaban is rapidly absorbed with maximum concentrations (C) appearing 3 to 4 hours after tablet intake. Apixaban can be taken with or without food.
Distribution: Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.
Biotransformation and elimination: Apixaban has multiple routes of elimination of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Apixaban has a total clearance of about 3.3L/h and a half-life of approximately 12 hours.
Elderly: (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher and no difference in C.
Renal impairment: Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity.
Hepatic impairment: Pharmacokinetics and pharmacodynamics of apixaban 5mg were not altered in subjects with hepatic impairment.
Gender and Body Weight: Exposure to apixaban was approximately 18% higher in females than in males. Compared to apixaban exposure in subjects with body weight of 65 to 85kg, body weight > 120kg was associated with approximately 30% lower exposure and body weight < 50kg was associated with approximately 30% higher exposure.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
AFIXBA™ tablet 2.5mg in a pack of 30's
AFIXBA™ tablet 5mg in a pack of 30's

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of the reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg Lic. No. 000072

ایفکسبا™ ٹیبلٹ
(اپیکسابان)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

120mm