215 X 150 mm

# Abaxil

**Tablets**
**2.5mg, 5mg**

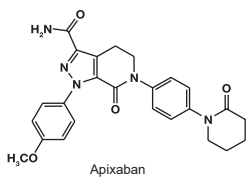
## (Apixaban M.S*)

# ابیکسل

ٹیبلٹس ۲.۵ ملی گرام ، ۵ ملی گرام

(اپیکسابین ایم۔ایس*)

**DESCRIPTION:**
Abaxil (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 $C_{25}$ $H_{25}$ $N_5$ $O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban

**COMPOSITION:**
Abaxil (Apixaban) Tablets are available for oral administration as:

Abaxil Tablets 2.5mg
Each film-coated tablet contains:
Apixaban M.S*.....2.5mg

Abaxil Tablets 5mg
Each film-coated tablet contains:
Apixaban M.S*.....5mg
*Manufacturer's Specs.

**CLINICAL PHARMACOLOGY:**

**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 Abaxil. Food does not affect the bioavailability of apixaban. Maximum concentrations ($C_{max}$) of apixaban appear 3 to 4 hours after oral administration of Abaxil. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets suspended in 30 mL of water, exposure was similar to that after oral administration of 2 intact 5 mg tablets. Following oral administration of 10 mg of apixaban as 2 crushed 5 mg tablets mixed with 30 g of applesauce, the $C_{max}$ and AUC were 20% and 16% lower, respectively, when compared to administration of 2 intact 5 mg tablets. Following administration of a crushed 5 mg Abaxil tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube, exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

***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.

**USE IN SPECIFIC POPULATIONS:**
**Pregnancy**
Risk Summary
The limited available data on Abaxil 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. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

*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 Abaxil, 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. Abaxil 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 [see Warnings and Precautions].

**Lactation**
*Risk Summary*
There are no data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. 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 Abaxil.

**Pediatric Use**
Safety and effectiveness in pediatric patients have not been established.

**Geriatric Use**
Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. 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 [see Dosage and Administration]
- 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

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with apixaban did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of Abaxil at the usually recommended dose [see Dosage and Administration] will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study see Clinical Pharmacology. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

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 [see Dosage and Administration]. Clinical efficacy and safety studies with apixaban did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis [see Clinical Pharmacology].

**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 [see Clinical Pharmacology].

Abaxil is not recommended in patients with severe hepatic impairment (Child-Pugh class C) [see Clinical Pharmacology]

215 X 150 mm

**INDICATIONS AND USAGE:**

***Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation***

Abaxil (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***

Abaxil (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
  Abaxil (Apixaban) is indicated for the treatment of DVT.
- Treatment of Pulmonary Embolism
  Abaxil (Apixaban) is indicated for the treatment of PE.
- Reduction in the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism

Abaxil (Apixaban) is indicated to reduce the risk of recurrent DVT and PE following initial therapy

**DOSAGE AND ADMINISTRATION:**

Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:

- The recommended dose is 5 mg orally twice daily.
- In patients with at least 2 of the following characteristics:
  age greater than or equal to 80 years, body weight less than or equal to 60 kg, or serum creatinine greater than or equal to 1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily.

Prophylaxis of DVT following hip or knee replacement surgery:

- The recommended dose is 2.5 mg orally twice daily.

Treatment of DVT and PE:

- The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Reduction in the risk of recurrent DVT and PE following initial therapy:

- The recommended dose is 2.5 mg taken orally twice daily.

**CONTRAINDICATIONS:**

- Active pathological bleeding
- Severe hypersensitivity to Abaxil (apixaban)

**ADVERSE REACTIONS:**

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased Risk of Thrombotic Events After Premature Discontinuation [see Warnings and Precautions]
- Bleeding [see Warnings and Precautions]
- Spinal/Epidural Anesthesia or Puncture [see Warnings and Precautions]

**WARNINGS AND PRECAUTIONS:**

**Increased Risk of Thrombotic Events after Premature Discontinuation**

Premature discontinuation of any oral anticoagulant, including Abaxil, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from Abaxil to warfarin in clinical trials in atrial fibrillation patients. If Abaxil is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [see Dosage and Administration].

**Bleeding**

Apixaban increases the risk of bleeding and can cause serious, potentially fatal, bleeding [see Dosage and Administration and Adverse Reactions]

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) [see Drug Interactions].
Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue Abaxil in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect
An agent to reverse the anti-factor Xa activity of apixaban is available. The pharmacodynamic effect of Abaxil 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 considered, but have not been evaluated in clinical studies [see Clinical Pharmacology].
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 [see Overdosage].
Hemodialysis does not appear to have a substantial impact on apixaban exposure [see Clinical Pharmacology]. 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) in individuals receiving Abaxil, and they are not expected to be effective as a reversal agent.

**Spinal/Epidural Anesthesia or Puncture**

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 Abaxil. The next dose of Abaxil 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 Abaxil 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.

**Patients with Prosthetic Heart Valves**

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

**Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy**

Initiation of Abaxil 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 Abaxil, 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.

**DRUG INTERACTIONS:**

- Combined P-gp and strong CYP3A4 inhibitors increase blood levels of apixaban. Reduce Abaxil dose or avoid coadministration.
- Simultaneous use of combined P-gp and strong CYP3A4 inducers reduces blood levels of apixaban: Avoid concomitant use.

**ANTICOAGULANT & ANTIPLATELETS AGENTS**

Co-administration of antiplatelets agents fibrinolyties, heparin, aspirin and chronic NSAID use increases the risk of bleeding.

**OVERDOSAGE:**

Overdose of Abaxil (Apixaban) increases the risk of bleeding [see Warnings and Precautions].
In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.
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. Thus, administration of activated charcoal may be useful in the management of Abaxil (Apixaban) overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

**INSTRUCTIONS:**

Store below 30°C.
Protect from moisture and direct sunlight.
Keep out of the reach of children.
To be sold on prescription of a registered medical practitioner only.

**PACK SIZE:**

**Abaxil 2.5mg Tablet:**
3x10's tablets in Alu-Alu blister pack.
**Abaxil 5mg Tablet:**
3x10's tablets in Alu-Alu blister pack.

خوراک:
دوا ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات:
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
نمی اور سورج کی روشنی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔

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