For use in india only

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Apixaban Tablets 2.5 mg/ 5 mg

MSN APIBAN 2.5/5 एम एस एन अपिबेन २.५/५

Not to be sold by retail without the prescription of a Registered Medical Practitioner.

PRESCRIBING INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF APIXABAN INCREASES THERISK OF THROMBOTIC EVENTS (B) SPINAL/EPIDURAL HEMATOMA

(A) 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.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with Apixaban who are receiving neuraxial aesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients 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**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of Apixaban and neuraxial procedures is not known**

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.

1. GENERIC NAME

Apixaban Tablets 2.5 mg
Apixaban Tablets 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Apixaban Tablets 2.5 mg
Each Film Coated Tablet contains
Apixaban….. 2.5 mg
Colours: Titanium Dioxide IP
Ferric Oxide Yellow -USP-NF

Apixaban Tablets 5 mg
Each Tablet contains
Apixaban ….. 5 mg
Colours: Titanium Dioxide IP
Ferric Oxide Red - USP-NF

3. DOSAGE FORM AND STRENGTH

Film coated tablets 2.5 mg and 5 mg.

4. CLINICAL PARTICULARS

4.1. Indications

Apixaban is indicated for:

- Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.
- 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.

4.2. Posology and Method of Administration

Prevention of VTE (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.
Physicians may consider the potential benefits of earlier anticoagulation for VTE prophylaxis as well as the risks of post-surgical bleeding in deciding on the time of administration within this time window.

- 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.

Dose reduction
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, 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 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, immobilisation).

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 or with another anticoagulant, as indicated in below table.

Table 1: Dose recommendation (VTEt)

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

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 Eliquis immediately and then continue with twice daily intake as before.

Switching
Switching treatment from parenteral anticoagulants to Apixaban (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
VTEp and VTEt – No dose adjustment required.

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 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, 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 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.

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.

Body weight
VTEp and VTEt - No dose adjustment required.

NVAF - No dose adjustment required, unless criteria for dose reduction are met.

Gender
No dose adjustment required.

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
Oral use

Apixaban should be swallowed with water, with or without food.

For patients who are unable to swallow whole tablets, Apixaban tablets may be crushed and suspended in water, or 5% glucose in water (G5W), or apple juice or mixed with apple puree and immediately administered orally. Alternatively, Apixaban tablets may be crushed and suspended in 60 mL of water or G5W and immediately delivered through a nasogastric tube.

Crushed Apixaban tablets are stable in water, G5W, apple juice, and apple puree for up to 4 hours.

4.3. Contraindications

Apixaban is contraindicated in patients with the following conditions:

- Hypersensitivity to the active substance or to any of the excipients used in the formulation.
- Severe hypersensitivity reaction to Apixaban (e.g., anaphylactic reactions)
- 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.

4.4. Special Warnings and Precautions for Use

Haemorrhage risk
As with other anticoagulants, patients taking apixaban are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Apixaban administration should be discontinued if severe haemorrhage occurs.
Although treatment with Apixaban does not require routine monitoring of exposure, a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of Apixaban exposure may help to inform clinical decisions, e.g., overdose and emergency surgery.

Reversal of Anticoagulant Effect
An agent to reverse the anti-factor Xa activity of Apixaban is available. The pharmacodynamic effect of ELIQUIS 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. 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

Interaction with other medicinal products affecting haemostasis
Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated.
The concomitant use of Apixaban with antiplatelet agents increases the risk of bleeding.
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.
Following surgery, other platelet aggregation inhibitors are not recommended concomitantly with Apixaban.
In patients with atrial fibrillation and conditions that warrant mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with Apixaban.

Use of thrombolytic agents for the treatment of acute ischemic stroke
There is very limited experience with the use of thrombolytic agents for the treatment of acute ischemic stroke in patients administered Apixaban.

Patients with prosthetic heart valves
Safety and efficacy of apixaban have not been studied in patients with prosthetic heart valves, with or without atrial fibrillation. Therefore, the use of apixaban is not recommended in this setting.

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.

Surgery and invasive procedures
Apixaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.

Apixaban should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled.

If surgery or invasive procedures cannot be delayed, appropriate caution should be exercised, taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

Apixaban should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established.

For patients undergoing catheter ablation for atrial fibrillation, apixaban treatment does not need to be interrupted.

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.

Spinal/epidural anaesthesia 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 (e.g., numbness or weakness of the legs, 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.

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.

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 since the safety and efficacy of apixaban have not been established in these clinical situations.

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.

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. For the prevention of VTE in elective hip or knee replacement surgery (VTEp), the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt), apixaban is to be used with caution in patients with severe renal impairment (creatinine clearance 15-29 mL/min).

For the prevention of stroke and systemic embolism in patients with NVAF, patients with severe renal impairment (creatinine clearance 15-29 mL/min), and patients with serum creatinine ≥ 1.5 mg/dL (133 micromole/L) associated with age ≥ 80 years or body weight ≤ 60 kg 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.

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.

Body weight
Low body weight (< 60 kg) may increase haemorrhagic risk.

Patients with 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.
It should be used with caution in patients with mild or moderate hepatic impairment (Child Pugh A or B).
Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin ≥ 1.5 x ULN were excluded in clinical studies. Therefore apixaban should be used cautiously in this population. Prior to initiating apixaban, liver function testing should be performed.

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). These medicinal products may increase Apixaban exposure by 2-fold, or greater in the presence of additional factors that increase Apixaban exposure (e.g., severe renal impairment).

Interaction with inducers of both CYP3A4 and P-gp
The concomitant use of Apixaban with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to a ~50% reduction in Apixaban exposure. In a clinical study in atrial fibrillation patients, diminished efficacy and a higher risk of bleeding were observed with coadministration of Apixaban with strong inducers of both CYP3A4 and P-gp compared with using Apixaban alone.

In patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp the following recommendations apply.

- ➢ for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE, apixaban should be used with caution;
- ➢ for the treatment of DVT and treatment of PE, apixaban should not be used since efficacy may be compromised.

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.

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. Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5. Drug Interactions

Inhibitors of CYP3A4 and P-gp
Coadministration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban C_{max}.

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).

Active substances which are not considered strong inhibitors of both CYP3A4 and P-gp, (e.g., 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 coadministered with agents that are not strong inhibitors of both CYP3A4 and P-gp. For example, diltiazem (360 mg once a day), considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean Apixaban AUC and a 1.3-fold increase in C_{max}. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean Apixaban AUC and C_{max}, respectively. Clarithromycin (500 mg, twice a day), an inhibitor of P-gp and a strong inhibitor of CYP3A4, led to a 1.6-fold and 1.3-fold increase in mean Apixaban AUC and C_{max} respectively.

Inducers of CYP3A4 and P-gp
Coadministration of Apixaban with rifampicin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean Apixaban AUC and C_{max}, respectively. The concomitant use of Apixaban with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced Apixaban plasma concentrations. No dose adjustment for Apixaban is required during concomitant therapy with such medicinal products, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp Apixaban should be used with caution for the prevention of VTE in elective hip or knee replacement surgery, for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE.

Apixaban is not recommended for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised.

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, 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.

After combined administration of enoxaparin (40 mg single dose) with Apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident when Apixaban was coadministered with ASA 325 mg once a day.

There is limited experience of co-administration with other platelet aggregation inhibitors (such as GPIIb/IIIa receptor antagonists, dipyridamole, dextran or sulfinpyrazone) or thrombolytic agents. As such agents increase the bleeding risk, co-administration of these medicinal products with apixaban is not recommended.

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when Apixaban was coadministered with atenolol or famotidine. Coadministration of Apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of Apixaban. Following administration of the two medicinal products together, mean Apixaban AUC and C_{max} were 15% and 18% lower than when administered alone. The administration of Apixaban 10 mg with famotidine 40 mg had no effect on Apixaban AUC or C_{max}.

Effect of Apixaban on other medicinal products
Apixaban has no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 μM) and has 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 showed no induction of CYP1A2, CYP2B6, 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.

Digoxin
Coadministration of Apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, has no effect on digoxin AUC or C_{max}. Therefore, Apixaban does not inhibit P-gp mediated substrate transport.

Naproxen
Coadministration of single doses of Apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or C_{max}.

Atenolol
Coadministration of a single dose of Apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

Activated charcoal
Administration of activated charcoal reduces Apixaban exposure.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy
There are no data from the use of Apixaban in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of Apixaban during pregnancy.

Breast-feeding
It is unknown whether Apixaban or its metabolites are excreted in human milk. Available data in animals have shown excretion of Apixaban in milk. A risk to the suckling child cannot be excluded.

A decision must be made whether to 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.

Fertility
Studies in animals dosed with Apixaban have shown no effect on fertility.

4.7. Effects on Ability to Drive and Use Machines

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

4.8. Undesirable Effects

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

- Increased risk of thrombotic events after premature discontinuation
- Bleeding
- Spinal/epidural anesthesia or puncture

Tabulated list of adverse reactions
Below table 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.

System organ class	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)	Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)	Treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)
Blood and lymphatic system disorders			
Anaemia	Common	Common	Common
Thrombocytopenia	Uncommon	Uncommon	Common
Immune system disorders			
Hypersensitivity, allergic oedema and Anaphylaxis	Rare	Uncommon	Uncommon
Pruritus	Uncommon	Uncommon	Uncommon
Angioedema	Not known	Not known	Not known
Nervous system disorders			
Brain haemorrhage†	Not known	Uncommon	Rare
Eye disorders			
Eye haemorrhage (including conjunctival haemorrhage)	Rare	Common	Uncommon
Vascular disorders			
Haemorrhage, haematoma	Common	Common	Common
Hypotension (including procedural hypotension)	Uncommon	Common	Uncommon
Intra-abdominal haemorrhage	Not known	Uncommon	Not known
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Uncommon	Common	Common
Haemoptysis	Rare	Uncommon	Uncommon
Respiratory tract haemorrhage	Not known	Rare	Rare
Gastrointestinal disorders			
Nausea	Common	Common	Common
Gastrointestinal haemorrhage	Uncommon	Common	Common
Haemorrhoidal haemorrhage	Not known	Uncommon	Uncommon
Mouth haemorrhage	Not known	Uncommon	Common
Haematochezia	Uncommon	Uncommon	Uncommon
Rectal haemorrhage, gingival bleeding	Rare	Common	Common
Retroperitoneal haemorrhage	Not known	Rare	Not known
Hepatobiliary disorders			
Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	Uncommon	Uncommon	Uncommon
Gamma-glutamyltransferase increased	Uncommon	Common	Common
Alanine aminotransferase increased	Uncommon	Uncommon	Common
Skin and subcutaneous tissue disorders			
Skin rash	Not known	Uncommon	Common
Alopecia	Rare	Uncommon	Uncommon
Erythema multiforme	Not known	Very rare	Not known
Musculoskeletal and connective tissue disorders			
Muscle haemorrhage	Rare	Rare	Uncommon
Renal and urinary disorders			
Haematuria	Uncommon	Common	Common
Reproductive system and breast disorders			
Abnormal vaginal haemorrhage, urogenital haemorrhage	Uncommon	Uncommon	Common
General disorders and administration site conditions			
Application site bleeding	Not known	Uncommon	Uncommon
Investigations			
Occult blood positive	Not known	Uncommon	Uncommon
Injury, poisoning and procedural complications			
Contusion	Common	Common	Common
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	Uncommon	Uncommon	Uncommon
Traumatic haemorrhage	Not known	Uncommon	Uncommon

† The term "Brain haemorrhage" encompasses all intracranial or intraspinal haemorrhages (i.e., haemorrhagic stroke or putamen, cerebellar, intraventricular, or subdural haemorrhages).

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 posthaemorrhagic anaemia. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +918458305295/+917331134745. By reporting side effects, you can help provide more information on the safety of this product.

4.9. Overdose

Overdose of Apixaban increases the risk of bleeding. Administration of activated charcoal may be useful in the management of Apixaban overdose or accidental ingestion.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

As a result of FXa inhibition, Apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of Apixaban.

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.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel. A 50% to 60% increase in anti-FXa activity was observed when Apixaban was coadministered with enoxaparin or naproxen.

Specific Populations
Renal impairment: Anti-FXa activity adjusted for exposure to Apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

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

5.3 PHARMACOKINETIC PROPERTIES

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 (C_{max}) of Apixaban appear 3 to 4 hours after oral administration of Apixaban. 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 Apixaban 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.

Drug Interaction Studies
In *in vitro* Apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, Apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

Specific Populations

Gender: A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

Race: The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. . The systemic exposures (AUCs) of unbound Apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound Apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Mutagenesis: Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Impairment of Fertility: Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in unbound apixaban exposure levels that are 3 and 4 times, respectively, the human exposure. Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring (F1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure to unbound apixaban that is 5 times the human exposure. Adverse effects in the F1-generation female offspring were limited to decreased mating and fertility indices at ≥200 mg/kg/day (a dose resulting in exposure to unbound apixaban that is ≥5 times the human exposure).

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

2's & 10's Blister pack

7.3 Storage and Handling Instructions

Do not store above 30^{0}C.

8. PATIENT COUNSELLING INFORMATION

Advise patients of the following:

- Not to discontinue Apixaban without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with Apixaban. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking Apixaban, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with Apixaban.
- How to take Apixaban if they cannot swallow, or require a nasogastric tube.
- What to do if a dose is missed.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division,
Unit II, Survey No. 1277 & 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy District, Pin Code: 509228,
Telangana, India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

5/MN/TS/2014/F/G, 26/08/2019

11. DATE OF REVISION

August 2022.

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