Apithromb

1. **Apixaban 2.5 / 5 mg tablets**
2. **Qualitative and Quantitative composition**

Apixaban……..	2.5 / 5 mg
Excipient…….	q.s.

3. Dosage Form and Strength:

Oral tablets containing Apixaban 2.5 / 5 mg

4. Clinical particulars

4.1 Therapeutic indication

- 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), including those with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age > 75 years; hypertension; diabetes mellitus
- Treatment of deep vein thrombosis (DVT) and pulmonary Embolism (PE), and prevention of Recurrent DVT and PE in adult patients.

4.2 Posology

The recommended dose is 5 mg tablet twice a day or as directed by physician.

4.3 Method of administration:

For oral administration only.

4.4 Contraindication

- 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.
- 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.

4.5 Special warnings and precautions for use

1) 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.

2) 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 drugs (NSAIDs), including acetylsalicylic acid.

3) 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.

4) 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.

5) 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.

6) 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.

7) 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.

8) 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.

9) 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.

10) 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.

11) 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).

12) 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.

4.6 Drug interactions

1) 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 Cmax. 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).

2) 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 Cmax, 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.

3) 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. 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 co-administered with ASA 325 mg once a day.

4) Other concomitant therapies: No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered 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.

5) 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, CYP3A4/5 at a concentration up to 20 µM. Therefore, apixaban is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Digoxin

Coadministration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or Cmax. 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 Cmax.

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.

4.7 Use in special population

1) 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.

2) 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.

3) Fertility: Studies in animals dosed with apixaban have shown no effect on fertility.

4.8 Effects on ability to drive and use machine

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

4.9 Undesirable effects

Common adverse reactions were haemorrhage, contusion, epistaxis, and haematoma.

4.10 Overdose

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.

5. Pharmacological properties

5.1 Mechanism of action

Apixaban is a potent, oral, reversible, direct and highly selective active site inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development.

5.2 Pharmacodynamic properties

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR and 15 activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban. In the thrombin generation assay, apixaban reduced endogenous thrombin potential, a measure of thrombin generation in human plasma.

5.3 Pharmacokinetic properties

1) Absorption: The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (Cmax) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or Cmax at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg.

2) Distribution: Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 litres.

3) 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. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively. Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major active substance-related component in human plasma with no active circulating metabolites present.

6. Nonclinical properties

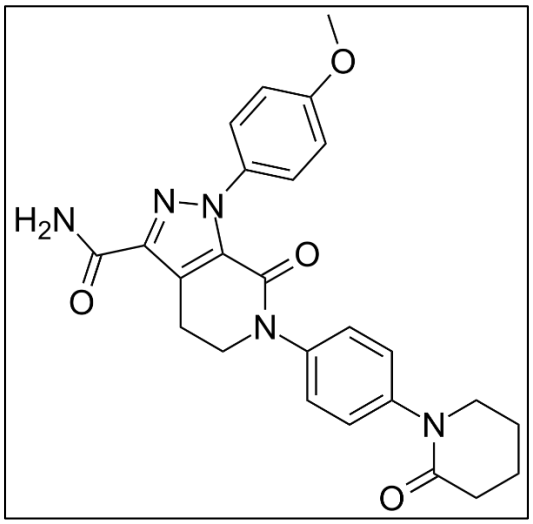
6.1 Animal Toxicology or Pharmacology

Not required.

7. Description

Apixaban is a pyrazolopyridine that is 7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide substituted at position 1 by a 4-methoxyphenyl group and at position 6 by a 4-(2-oxopiperidin-1-yl)phenyl group. with the empirical formula C25H25N5O4 459.497 g/mol ,

a molecular weight of 121.18, and the following structural formula:



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Apixaban is available as 2.5 / 5 mg tablets

8.4 Storage and handling instructions

Store at 20°C to 25°C (68°F-77°F)

9. Patient Counselling Information

9.1 Adverse reactions

Refer part 3.8

9.2 Drug Interactions

Refer part 3.5

9.3 Dosage

Refer part 3.2

9.4 Storage

Refer part 7.4

9.5 Risk factors

Refer part 3.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 3.4

10. Manufactured by: Pure and Cure Healthcare Pvt. Ltd

11. Manufacturer lic no: 31/UK/2013

12. Date of revision: July 2023