APIXATOR

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

abbreviated prescribing information for APIXATOR (Apixaban 2.5 mg and 5 mg film coated tablet) [Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES: 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. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserved haemostasis.

INDICATION: Apixator used for Prevention of stroke and systemic embolism in adult patients with non-valvular artrial fibrillation (NVAF), including those with one or more risk factors, such as prior stroke or transient ischemic attack.

Treatment of deep vein thrombosis (DVT) and pulmonary Embolism (PE), and prevention of Recurrent DVT and PE in adult patients.

DOSAGE AND ADMINISTRATION: Dosage: Apixator 2.5 mg and 5 mg film coated tablet. **Administration:** As directed by the Physician. Tablets should be taken orally.

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. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Concomitant treatment with any other anticoagulant agent e.g., unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, rivaroxaban, dabigatran, etc.) except under specific circumstances of switching anticoagulant therapy, when UFH is given at doses necessary to maintain an open central venous or arterial catheter or when UFH is given during catheter ablation for atrial fibrillation.

WARNINGS & PRECAUTIONS: *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. *Interaction with other medicinal products affecting haemostasis:* 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. *Use of thrombolytic agents for the treatment of acute ischemic stroke, prosthetic heart valves:* the use of apixaban is not recommended in this setting. *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. *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. *Temporary discontinuation:* Discontinuing anticoagulants, including apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis.

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. *Patients with active cancer*: can be at high risk of both venous thromboembolism and bleeding events. *Renal impairment:* 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, Body weight* may increase haemorrhagic risk. *Hepatic impairment:* Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. *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).

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 and HIV protease inhibitors. *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. 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 co-administration of these medicinal products with apixaban is not recommended. *apixaban on other medicinal products:* apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

ADVERSE REACTIONS: *Blood and lymphatic system disorders:* Common: Anaemia, uncommon: Thrombocytopenia. *Immune system disorders:* Uncommon: Hypersensitivity, allergic oedema and Anaphylaxis, Pruritus, Not known: Angioedema. *Nervous system disorders:* Uncommon: Brain haemorrhage. *Eye disorders:* Eye haemorrhage (including conjunctival haemorrhage). *Vascular disorders*: Common: Haemorrhage, haematoma, Hypotension (including procedural hypotension), Intra-abdominal haemorrhage. *Respiratory, thoracic and mediastinal disorders:* Common: Epistaxis, Uncommon: Haemoptysis, Rare: Respiratory tract haemorrhage. *Gastrointestinal disorders:* Common: Nausea, Gastrointestinal haemorrhage. Uncommon: Haemorrhoidal haemorrhage, Mouth haemorrhage, Haematochezia. Rare: Retroperitoneal haemorrhage. *Hepatobiliary disorders:* Common: Gamma-glutamyltransferase increased. Uncommon: Liver function test abnormal, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, Alanine aminotransferase increased. *Skin and subcutaneous tissue disorders:* Uncommon: Skin rash. Alopecia. Very rare: Erythema multiforme. Not known: Cutaneous vasculitis. *Musculoskeletal and connective tissue disorders:* Rare: Muscle haemorrhage. *Renal and urinary disorders*: Common: Haematuria. *Reproductive system and breast disorders*: Abnormal vaginal haemorrhage, urogenital haemorrhage. *General disorders and administration site conditions:* Uncommon: Application site bleeding *Investigations:* Uncommon: Occult blood positive. *Injury, poisoning and procedural complications*: Common: Contusion. Uncommon: 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: Traumatic haemorrhage.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

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(Additional information is available on request)