SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Advaxaban Tablets 2.5 mg (Apixaban)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Apixaban, MDM ..... 2.5 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Advaxaban is a factor Xa inhibitor indicated in:

- Prevention of venous thromboembolic events (VTE), which may lead to pulmonary embolism (PE), in patients who have undergone elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischemic 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 following initial therapy.

4.2 Posology and method of administration

DOSAGE AND 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. Recommended duration of treatment:

- In patients undergoing hip replacement surgery: 32 to 38 days.
- In patients undergoing knee replacement surgery: 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. 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.

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. The recommended dose of Apixaban for the prevention of recurrent DVT and PE is 2.5 mg taken orally twice daily.

Missed dose

If a dose is missed, the patient should take Advaxaban immediately and then continue with twice daily intake as before.

Switching

Switching treatment from parenteral anticoagulants to Advaxaban (and vice versa) can be done at the next scheduled dose. These medicinal products should not be administered simultaneously.

When converting patients from vitamin K antagonist (VKA) therapy to Advaxaban, warfarin or other VKA therapy should be discontinued and Advaxaban started when the international normalized ratio (INR) is < 2.

When converting patients from Advaxaban to VKA therapy, administration of Advaxaban should be continued for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Advaxaban with VKA therapy, an INR should be obtained prior to the next scheduled dose of Apixaban. Co-administration of Advaxaban and VKA therapy should be continued until the INR is ≥ 2.

Paediatric population

The safety and efficacy of Advaxaban in children and adolescents below age 18 have not been established. No data are available.

Renal impairment

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 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

Advaxaban 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.

4.3 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.
- Concomitant treatment with any other anticoagulant agent except under specific circumstances of switching anticoagulant therapy or 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

- Hemorrhage risk: Apixaban can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. Discontinue if severe hemorrhage occurs.
- Prosthetic heart valves: Apixaban use not recommended.
- Advaxaban should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding.
- Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome: Advaxaban use not recommended.
- Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of Apixaban.
- Safety and efficacy of Apixaban have not been established in hemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy and in patients with active cancer.
- Apixaban is not recommended in patients undergoing hip fracture surgery.

4.5 Interaction with other medicinal products and other forms of interaction

Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce Apixaban dose or avoid coadministration. Simultaneous use of strong dual inducers of CYP3A4 (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) and P-gp reduces blood levels of apixaban: Avoid concomitant use.

Anticoagulants, platelet aggregation inhibitors and NSAIDs: Due to an increased bleeding risk, concomitant treatment with any other anticoagulants is contraindicated. Medicinal products associated with serious bleeding are not recommended concomitantly with Apixaban such as: thrombolytic agents, fibrinolytics, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran, heparin, aspirin, chronic NSAID and sulfinpyrazone.

4.6 Fertility, pregnancy and lactation

Pregnancy

Not recommended.

Lactation

Discontinue drug or discontinue nursing taking into account the benefit ratio of therapy.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

For these conditions, the most common general adverse effect of Apixaban is bleeding which may be potentially life threatening and require immediate medical attention.

In prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery (VTEp)

Common: Anemia, Haemorrhage, haematoma, Epistaxis, Nausea, Contusion.

Uncommon: Thrombocytopenia, Pruritus, Hypotension (including procedural hypotension), Epistaxis, Gastrointestinal haemorrhage, Haematochezia, Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, Gamma-glutamyl transferase

increased, Alanine aminotransferase increased, Haematuria, Abnormal vaginal haemorrhage, urogenital haemorrhage, Occult blood positive, 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.

In prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors (NVAF)

Common: Anaemia, Eye haemorrhage (including conjunctival haemorrhage), Nausea, Gastrointestinal haemorrhage, Rectal haemorrhage, gingival bleeding, Gamma-glutamyl transferase increased, Haematuria, Contusion.

Uncommon: Thrombocytopenia, Hypersensitivity, allergic oedema and Anaphylaxis, Pruritus, Brain haemorrhage, Intra-abdominal haemorrhage, Haemoptysis, Haemorrhoidal haemorrhage, Mouth haemorrhage, Haematochezia, Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, Alanine aminotransferase increased, Skin rash, Abnormal vaginal haemorrhage, urogenital haemorrhage, Application site bleeding, Occult blood positive, 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, Traumatic haemorrhage.

In treatment of DVT and PE, and prevention of recurrent DVT and PE (VTEt)

Common: Anaemia, Epistaxis, Nausea, Gastrointestinal haemorrhage, Mouth haemorrhage, Rectal haemorrhage, gingival bleeding, Gamma-glutamyl transferase increased, Alanine aminotransferase increased, Haematuria, Skin rash, Abnormal vaginal haemorrhage, urogenital haemorrhage, Contusion.

Uncommon: Hypersensitivity, allergic oedema and Anaphylaxis, Pruritus, Eye haemorrhage (including conjunctival haemorrhage), Hypotension (including procedural hypotension), Haemoptysis, Haemorrhoidal haemorrhage, Haematochezia, Liver function test abnormal, asparate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, Application site bleeding, Occult blood positive, 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, Traumatic haemorrhage.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse reactions via the pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

There is no antidote to Apixaban. Overdose of Advaxaban may result in a higher risk of bleeding. In the event of hemorrhagic complications, treatment must be discontinued, and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical hemostasis or the transfusion of fresh frozen plasma 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.

Pharmacodynamics

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.

The Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF. This test is not recommended for assessing the anticoagulant effect of apixaban.

5.2 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 (Cmax) of apixaban appear 3 to 4 hours after oral administration of APIXABAN.

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. 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.

5.3 Preclinical safety data

Not Applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not specified in available data.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

02 years (24 Months)

6.4 Special precautions for storage

Store below 30°C.

Protect from light, heat and moisture.

Keep all medications out of the reach of children.

6.5 Nature and contents of container

Available in 3x10's film-coated tablets in blister.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Manufactured by: MARTIN DOW MARKER LTD

Address: 7, Jail Road, Quetta, Pakistan.

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

22-08-2026