PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

ELIQUIS® 2.5 mg
Film-coated tablets

Apixaban 2.5 mg

ELIQUIS® 5 mg
Film-coated tablets

Apixaban 5 mg

For a list of inactive and allergens in this preparation, see section 2 under "Important information about some of this medicine's ingredients" and section 6 "Further information".
Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar to yours.

This medicine is not intended for treatment of children and adolescents under 18 years of age.

Patient safety information card:
This card contains important safety information that you must be aware of, before starting, and during treatment, with **Eliquis®**.
The card contains information intended for both the patient and the medical staff. It provides patient guidance as to how to minimize the risk of bleeding arising from treatment with each of the anticoagulants.
In addition, the card contains personal patient information and information about **Eliquis®**.
Present this card to each medical staff member involved in your treatment.

1. WHAT IS THE MEDICINE INTENDED FOR?

Eliquis® 2.5 mg
For prevention of venous thrombotic events in adult patients following elective hip or knee replacement surgery.
For prevention of stroke and embolism in adult patients with atrial fibrillation (of a non-valvular source) and with at least one risk factor, such as: prior stroke or transient ischemic attack, aged 75 years and above, hypertension, diabetes mellitus, symptomatic heart failure.
For treatment of blood clots in the veins of the legs (deep-vein thrombosis) and in the blood vessels of the lungs (pulmonary embolism), and to prevent recurrence of blood clots in these blood vessels.

Eliquis® 5 mg
For prevention of stroke and embolism in adult patients with atrial fibrillation (of a non-valvular source) and with at least one risk factor, such as: prior stroke or transient ischemic attack, aged 75 years and above, hypertension, diabetes mellitus, symptomatic heart failure.
For treatment of blood clots in the veins of the legs (deep-vein thrombosis) and in the blood vessels of the lungs (pulmonary embolism).

Therapeutic group
Anticoagulant

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the additional ingredients contained in the medicine, detailed in section 6.
- You are suffering from significant active bleeding.
- You are suffering from a liver disease causing a coagulation disturbance and risk of bleeding.
- You are suffering from an injury or a medical condition with an increased risk of bleeding, e.g., active stomach or bowel ulcer or one that has recently occurred, a malignant tumor with increased risk of bleeding, recent brain injury or spinal cord injury, recent intracranial bleeding, known or suspected esophageal varices, arteriovenous malformation, vascular aneurysm or major cerebral or spinal blood vessel abnormality.
- You have recently undergone brain, spine or eye surgery.
- You are taking other anticoagulants, such as: oral anticoagulants (e.g., warfarin, rivaroxaban, dabigatran), heparin, low molecular weight heparin (e.g., enoxaparin, dalteparin), heparin derivatives (such as: fondaparinux), excluding situations when switching from or to treatment with **Eliquis®** or if a venous or arterial line is installed and heparin needs to be administered through this line to keep it open.

Special warnings regarding use of the medicine:

- This medicine may cause changes in blood tests.

Before treatment with Eliquis®, tell the doctor if:

- You are breastfeeding.
- You are suffering from a severe kidney disease or if you are undergoing dialysis.
- You are suffering, or have suffered in the past, from impaired liver function. Caution is required in patients with signs of altered liver function.
- You are suffering from a medical condition that may increase the risk of bleeding, such as: a bleeding disorder, including a reduction in the activity of platelets, severe hypertension that is not controlled by medicinal treatment.
- You are older than 75 years, if you weigh 60 kg or less.
- You have had a catheter inserted or received an injection into the spine (for anesthesia or analgesia) in proximity to administration of the medicine.
  The doctor will instruct you to take the medicine 5 or more hours after the removal of the catheter.
- You have a prosthetic heart valve.
- Your doctor has determined that your blood pressure is unstable or that another treatment or surgical procedure to remove the blood clot from your lungs is planned.
- You are sensitive to any type of food or medicine.
- You are suffering from a congenital problem of galactose intolerance, Lapp-lactase deficiency or glucose-galactose malabsorption.
- You are scheduled to undergo surgery or treatment that may cause bleeding. As a result, you may be asked by the doctor to stop treatment with this medicine for a short while. If you are uncertain whether the treatment can cause bleeding, consult the doctor.
- You are suffering from antiphospholipid syndrome (a disorder of the immune system that increases the risk of blood clots). Your doctor may decide to change the treatment.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor, pharmacist or nurse. In particular, inform the doctor, pharmacist or nurse if you are taking:

- The following medicines may enhance the effect of **Eliquis®** and increase the risk of undesirable bleeding:
  - Certain medicines used to treat fungal infections (e.g., ketoconazole, itraconazole, voriconazole and posaconazole).
  - Certain medicines used to treat acquired immunodeficiency syndrome (HIV/AIDS) (e.g., ritonavir).
  - Medicines that are used to treat hypertension or heart problems (e.g., diltiazem).
  - Other medicines that are used to reduce formation of blood clots (e.g., enoxaparin).
  - Anti-inflammatory agents or pain medicines such as: naproxen or aspirin, especially if you are older than 75 years of age and are taking aspirin, you are at increased risk for bleeding.
  - Antidepressants from the selective serotonin reuptake inhibitor class (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs).
- The following medicines may decrease the concentration of **Eliquis®** in the blood and may thereby reduce its efficacy: medicines to treat tuberculosis or other infections (e.g., rifampin - an antibiotic), medicines to treat epilepsy or seizures (e.g., phenytoin, phenobarbital and carbamazepine), *Hypericum* (St. John's Wort), a herbal supplement used for depression.

Use of the medicine and food
The medicine can be taken with or without food.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, suspect you are pregnant or are planning a pregnancy, consult the doctor before starting treatment with any medicine.

The effects of **Eliquis®** on pregnancy or on the unborn baby are unknown.
Do not use **Eliquis®** if you are pregnant. If you become pregnant while using the medicine, **contact the doctor immediately.**

If you are breastfeeding, consult a doctor, pharmacist or nurse before using **Eliquis®**. It is not known whether **Eliquis®** passes into breast milk. The medical staff will tell you to either stop breastfeeding or to stop / not to start treatment with **Eliquis®**.

Important information about some of the ingredients of the medicine
The tablet contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to certain sugars, consult with your doctor before taking this medicine.
This medicine contains less than 1 mmol (23 mg) of sodium per capsule, meaning it is considered 'sodium free'.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

- The dosage and treatment regimen will be determined by the doctor only.
- Manner of administration: swallow the medicine with water.
- If you have difficulty swallowing the tablet whole, talk to your doctor about other possible ways to take **Eliquis®**. The tablet may be crushed and mixed with water, 5% glucose in water, apple juice or apple puree, immediately before you take it.
  Instructions for crushing:
  - Crush the tablet with a pestle and mortar.

- Carefully transfer all the powder into a suitable container, and mix with a little liquid, approximately 30 mL (2 tablespoons) water or one of the other liquids mentioned above.
- Swallow the mixture.
- Rinse the pestle and mortar you used for crushing the tablet, with a little water or one of the other liquids (30 mL), into the container that contained the mixture, and swallow the rinse.

If necessary, your doctor may give you **Eliquis®** through a nasogastric tube.

Do not exceed the recommended dose.

- **Treatment for prevention of venous thrombotic events in adult patients following elective hip or knee replacement surgery:**
  The recommended dosage is one tablet of **Eliquis®** 2.5 mg twice a day. For example, one tablet in the morning and another tablet in the evening.
  Try to take the medicine at regular times every day, in order to obtain the optimal effect of the treatment.
  Start taking the medicine about 12-24 hours following the surgery. Do not stop taking the medicine unless you have been told to do so by the doctor.
  The standard duration of treatment is 32-38 days following hip surgery, or 10-14 days following knee surgery.

- **Treatment for prevention of stroke and embolism in adult patients with atrial fibrillation (of a non-valvular source) and with at least one risk factor, such as: previous stroke or transient ischemic event, 75 years of age and above, hypertension, diabetes mellitus, symptomatic heart failure:**
  The recommended dosage is one tablet of **Eliquis®** 5 mg, twice a day. The recommended dosage will be reduced to 2.5 mg, twice a day, if:
  - You have severely reduced kidney function.
  - Two or more of the following criteria apply to you:
    Your blood tests indicate poor kidney function (value of serum creatinine is ≥ 1.5 mg/dL).
    You are 80 years old or older.
    Your weight is 60 kg or lower.

  The recommended dosage is one tablet, twice a day. For example, one tablet in the morning and another tablet in the evening. Try to take the medicine at regular times every day, in order to obtain the optimal effect of the treatment.
  Your doctor will decide how long you should continue treatment.

- **Treatment of blood clots in the veins of the legs and in the blood vessels of the lungs:**
  The recommended dosage is **two tablets** of **Eliquis® 5 mg**, twice a day for the first 7 days, for example: two tablets in the morning and two tablets in the evening.
  After the first 7 days of treatment, the recommended dosage is **one tablet** of **Eliquis® 5 mg**, twice a day, for example: one tablet in the morning and another tablet in the evening. Try to take the medicine at regular times every day, in order to obtain the optimal effect of the treatment.

- **For preventing blood clots from recurring following completion of 6 months of treatment:**
  The recommended dosage is **one tablet** of **Eliquis® 2.5 mg**, twice a day. For example, one tablet in the morning and another tablet in the evening.
  Try to take the medicine at regular times every day, in order to obtain the optimal effect of the treatment.

Your doctor will decide how long you should continue treatment.

Your doctor may prescribe the following changes in your anticoagulant treatment:
- Switching from treatment with **Eliquis®** to treatment with other anticoagulants:
  Stop taking **Eliquis®** and start treatment with the other anticoagulant (e.g., heparin) at the time you would have taken the next dose of **Eliquis®**.
- Switching from another anticoagulant to treatment with **Eliquis®**:
  Stop treatment with the anticoagulant and start treatment with **Eliquis®** at the time you would have had the next dose of the anticoagulant medicine you were taking. Then, continue as per the recommended dosage.
- Switching from treatment with vitamin K antagonists (e.g., warfarin) to treatment with **Eliquis®**:
  Stop treatment with the vitamin K antagonists. The doctor must perform blood tests and instruct you when to start treatment with **Eliquis®**.
- Switching from **Eliquis®** treatment to treatment with vitamin K antagonists (e.g., warfarin):
  If your doctor instructs you to start treatment with vitamin K antagonists (e.g., warfarin), continue taking **Eliquis®** for at least two more days after taking the first dose of the vitamin K antagonist. The doctor must perform blood tests and tell you when treatment with **Eliquis®** should be terminated.

Tests and follow-up
Before you start to use the medicine, the doctor will refer you for liver function tests.

If you took an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you. An overdose may cause bleeding. In case of bleeding, you may need a blood transfusion or surgery.

If you forgot to take this medicine at the specified time, take a dose as soon as you remember, and take the next dose at the regular time. Then continue as per the recommended dosage. If you are not sure what to do or have missed more than one dose, consult the doctor, pharmacist or nurse.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor or the pharmacist.
If you stop taking the medicine too early, you may suffer from the development of blood clots.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the doctor, pharmacist or nurse.

4. SIDE EFFECTS

As with any medicine, use of **Eliquis®** may cause side effects in some users.
Do not be alarmed when reading the list of side effects. You may not suffer from any of them. Side effects and their frequency can vary between the different indications and are detailed below for each indication. The most common side effect of **Eliquis®** is bleeding, which can be life-threatening and therefore requires immediate referral to a doctor.

Side effects characteristic of Eliquis® administration to prevent venous thrombotic events in adult patients following elective hip or knee replacement surgery:

Common side effects (may affect up to 1 in 10 people):
- Anemia, which may cause tiredness and paleness.
- Bleeding, including bruising and swelling.
- Nausea (feeling sick).

Uncommon side effects (may affect up to 1 in 100 people):
- Reduced number of platelets in your blood (may affect clotting).
- Bleeding, including: bleeding occurring after a surgery, including bruising and swelling, blood or liquid leaking from the incision or injection site. Bleeding in the stomach, bowel or red/bright blood in the stools, blood in the urine, nosebleed, vaginal bleeding.
- A decrease in blood pressure that may cause a feeling of faintness or have a quicker heartbeat.
- Blood test changes that may show: abnormal liver function results, increase in liver enzymes, increase in bilirubin - a breakdown product of red blood cells manifested by yellowing of the skin and eyes.
- Itching.

Rare side effects (may affect up to 1 in 1,000 people):
- Allergic reaction (hypersensitivity) which may cause swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Refer to the doctor immediately if you experience any of these symptoms.**
- Bleeding into the muscle, bleeding in the eye, bleeding from the gums and bloody cough, rectal bleeding, hair loss.

Side effects of unknown frequency (their frequency cannot be estimated from the existing data):
- Bleeding, including: bleeding in the brain, intraspinal bleeding, bleeding in the lungs or throat, bleeding in the mouth, bleeding into the abdominal cavity or into the space behind the abdominal cavity, bleeding from hemorrhoids, tests that show blood in the stools or urine.
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*).

Side effects characteristic of Eliquis® administration to prevent stroke and embolism in adult patients with atrial fibrillation (of a non-valvular source) and with at least one additional risk factor:

Common side effects (may affect up to 1 in 10 people):
- Bleeding, including: bleeding in the eyes, bleeding in the stomach or bowel, rectal bleeding, blood in the urine, nosebleed, bleeding from the gums, bruising and swelling.
- Anemia, which may cause tiredness or paleness.
- Low blood pressure, which may cause a feeling of faintness or have a quicker heartbeat.
- Nausea (feeling sick).
- Blood tests which may show an increase in gamma-glutamyl transferase (GGT).

Uncommon side effects (may affect up to 1 in 100 people):
- Bleeding, including: bleeding in the brain, intraspinal bleeding, bleeding in the mouth, bloody cough, bleeding into the abdominal cavity, vaginal bleeding, bright/red blood in the stools, bleeding occurring after a surgery, including bruising and swelling, blood or

liquid leaking from the incision or injection site, bleeding from hemorrhoids, tests that show blood in the stools or urine.
- Reduced number of platelets in your blood (may affect clotting).
- Blood test changes that may show: abnormal liver function results, increase in liver enzymes, increase in bilirubin - a breakdown product of red blood cells manifested by yellowing of the skin and eyes.
- Skin rash.
- Itching.
- Hair loss.
- Allergic reaction (hypersensitivity) which may cause swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Refer to the doctor immediately if you experience any of these symptoms.**

Rare side effects (may affect up to 1 in 1,000 people):
- Bleeding in the lungs or throat, bleeding into the space behind the abdominal cavity, bleeding into the muscle.

Very rare side effects (may affect up to 1 in 10,000 people):
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*).

The following side effects are known if you take Eliquis® for treatment or prevention of recurrence of blood clots in the veins of the legs or in the blood vessels of the lungs:

Common side effects (may affect up to 1 in 10 people):
- Bleeding, including: nosebleed, bleeding from the gums, blood in the urine, bruising and swelling, bleeding in the stomach, bleeding in the bowel and bleeding in the rectum, bleeding in the mouth, vaginal bleeding.
- Anemia, which may cause tiredness or paleness.
- Reduced number of platelets in your blood (may affect clotting).
- Nausea (feeling sick).
- Skin rash.
- Blood tests which may show an increase in gamma-glutamyl transferase (GGT) or alanine aminotransferase (ALT).

Uncommon side effects (may affect up to 1 in 100 people):
- Low blood pressure, which may cause a feeling of faintness or a quicker heartbeat.
- Bleeding, including: bleeding in the eyes, bleeding in the mouth or bloody cough, red/bright blood in the stools, tests showing blood in the stools or urine, bleeding as a result of surgery, including bruising and swelling, blood or liquid leaking from the incision or injection site, bleeding from hemorrhoids, bleeding into the muscle.
- Itching.
- Hair loss.
- Allergic reaction (hypersensitivity) which may cause swelling of the face, lips, mouth, tongue and/or throat and difficulty breathing. **Refer to the doctor immediately if you experience any of these symptoms.**
- Blood test changes that may show: abnormal liver function results, increase in liver enzymes, increase in bilirubin - a breakdown product of red blood cells manifested by yellowing of the skin and eyes.

Rare side effects (may affect up to 1 in 1,000 people):
- Bleeding, including: bleeding in the brain or in the spinal column, bleeding in the lungs.

Side effects of unknown frequency (the frequency cannot be estimated from the existing data):

- Bleeding, including: bleeding into the abdominal cavity or into the space behind the abdominal cavity.
- Skin rash which may form blisters and looks like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge) (*erythema multiforme*).

If a side effect occurred, if one of the side effects worsens, or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store at a temperature below 30°C. Store in the original package.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  Tablet core: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate.
  Film coat: hypromellose, lactose monohydrate, titanium dioxide, triacetin, 2.5 mg - iron oxide yellow, 5 mg - iron oxide red.

Each film-coated 2.5 mg tablet contains:
51.4 mg lactose and 0.08 mg sodium.
Each film-coated 5 mg tablet contains:
102.9 mg lactose and 0.16 mg sodium.

- 2.5 mg - A round (5.95 mm in diameter), film-coated yellow tablet. "893" is debossed on one side and "2½" on the other side.
- 5 mg - An oval (9.73 mm * 5.16 mm), film-coated pink tablet. "894" is debossed on one side and "5" on the other side.

License holder and its address: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

Drug registration numbers in the National Drug Registry of the Ministry of Health:
Eliquis® 2.5 mg: 148.31.33496
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