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

The medicine is dispensed with a doctor's prescription only

Lixiana 15 mg
Lixiana 30 mg
Lixiana 60 mg

Film coated tablets

Each film-coated tablet contains 15, 30 or 60 mg edoxaban, respectively.

For a list of inactive and allergenic ingredients in the preparation, see 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, consult your doctor or pharmacist.

This medicine has been prescribed to treat your illness - Do not pass it on to others. It may harm them even if it seems to you that their illness is similar.

In addition to the leaflet, there is a patient safety information card for Lixiana

This card contains important safety information which you should be aware of and follow prior to starting treatment and during the course of treatment with Lixiana.

The patient leaflet and patient safety information card must be read before starting use of the preparation.

Keep the card handy for further review as the need arises.

1. WHAT IS THE MEDICINE INTENDED FOR?

Lixiana is intended for:

- The prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) who have one or more additional risk factors, such as congestive heart failure, hypertension, age of 75 and above, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

- For treatment and prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults.

Therapeutic group: Antithrombotic drugs, direct factor Xa inhibitors in the coagulation cascade.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to **edoxaban** or to any of the other ingredients contained in the medicine (see section 6 “Further information”)
- You are actively bleeding
- You have an illness or medical condition that poses an increased risk of severe bleeding (such as a stomach ulcer, brain injury or hemorrhage, or recent brain or eye surgery)
- You are taking other medicines to prevent blood clotting (such as heparin, enoxaparin, dalteparin, fondaparinux, warfarin, dabigatran, rivaroxaban, or apixaban), except when changing the anticoagulant treatment, or while getting heparin through a venous or arterial line to keep it open.
- You have a liver disease which leads to an increased risk of hemorrhages
- You suffer from uncontrolled high blood pressure
- You are pregnant or breastfeeding.

Special warnings regarding use of the medicine

Before treatment with Lixiana tell your doctor:

- If you are at increased risk of bleeding from any of the following conditions:
- Endstage kidney disease or if you are on dialysis
- Severe liver disease
- Bleeding disorders
- Retinopathy - retinal disorder (vascular problem in the back of your eyes)
- Recent bleeding in the brain (intracranial or intracerebral)
- Vascular problems in the brain or spinal column

- If you have a mechanic heart valve
- Lixiana 15 mg is intended exclusively for transitioning from treatment with Lixiana 30 mg to treatment with a vitamin K antagonist (such as warfarin).

Pay particular attention and tell your doctor

- If you are aware that you suffer from a disorder called antiphospholipid syndrome (a disorder of the immune system that poses an increased risk of blood clot formation), your doctor will decide if the treatment must be altered.

If you need to have surgery

- It is very important to take Lixiana before and after the surgery at the precise times instructed by your doctor. If possible, stop taking Lixiana at least 24 hours prior to the surgery. Your doctor will decide when you should resume the treatment with Lixiana. In emergency situations, your doctor will help determine how to proceed with Lixiana.

If you suffer from an active cancer
The safety and efficacy of Lixiana in the treatment and/or prevention of venous thrombosis (VTE) has not been established.

In the elderly population
Exercise caution in giving Lixiana concurrently with acetylsalicylic acid (aspirin) due to the increased risk of hemorrhages.

Children and adolescents
Lixiana is not intended for children or adolescents under 18 years of age. No information is available about the use of the medicine in children and adolescents.

Tests and follow-up

During the period of treatment, a need may arise for testing haemoglobin and hematocrit levels in order to reveal occult bleeding.

Although use of Lixiana does not require follow-up tests, its anticoagulant effect can be assessed by means of an anti-factor Xa test. This information can be helpful when clinical decisions are needed in emergency situations.

Drug interactions:

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

- Any of the following medicines which are likely **to intensify the effect of Lixiana** and may increase the risk of unwanted bleeding:
  - Medicines for the treatment of fungal infections (such as: ketoconazole)

- Medicines to treat abnormal heart beat (such as: dronedarone, quinidine, verapamil)
- Other anticoagulant medicines (such as: heparin, clopidogrel or vitamin K antagonists such as warfarin, acenocoumarol, phenprocoumon, or dabigatran, rivaroxaban, apixaban)
- Antibiotic medicines (such as: erythromycin, clarithromycin)
- Medicines for the prevention of organ rejection after transplantation (such as: cyclosporine)
- Anti-inflammatories or analgesics (such as: naproxen or aspirin)
- Antidepressants of the SSRI or SNRI groups

In these cases your doctor will decide if you are to be treated with Lixiana and if follow-up is required.

- Any of the following medicines which are likely **to weaken the effect of Lixiana**
  - Certain medicines for the treatment of epilepsy (such as: phenytoin, carbamazepine, phenobarbital)
  - The Hypericum plant, St. John's Wort, used for states of anxiety and mild depression
  - An antibiotic medicine: rifampicin

In these cases your doctor will decide if you are to be treated with Lixiana and if follow-up is required.

Using this medicine with food
Lixiana may be taken with or without food.

Pregnancy, breastfeeding and fertility
Do not take Lixiana if you are pregnant or breastfeeding.
Use a reliable contraceptive while using Lixiana if there is a chance of you getting pregnant.
Tell your doctor immediately if you get pregnant during the treatment with Lixiana. He/She will decide how to treat you.

Driving and using machines
Lixiana has little or no effect on your ability to operate machines or drive.

3. HOW TO USE THIS MEDICINE?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually:

one 60 mg tablet once daily.

- **If you have impaired kidney function,** your doctor may reduce the dose to one 30 mg tablet once daily.
- **If your body weight is 60 mg or lower,** the recommended dose is one 30 mg tablet once daily.
- **If your doctor has prescribed you medicines known to be P-gp inhibitors**, such as cyclosporine, dronedarone, erythromycin, or ketoconazole, the usual dose is one 30 mg tablet once daily.

Do not exceed the recommended dose.

Method of administration
Swallow the tablet, preferably with water.
It can be taken with or without food.

If you have difficulty swallowing the tablet whole, talk to your doctor about other ways to take Lixiana. The tablet may be crushed and mixed with water or apple puree immediately before you take it. If necessary, your doctor may also give you the crushed Lixiana tablet through a stomach tube.

Your doctor may likely change your anticoagulant drug therapy as follows:

- *Transitioning from a vitamin K antagonist (for example, warfarin) to Lixiana:*
  - Stop taking the vitamin K antagonist (for example, warfarin). Your doctor will take blood measurements and will instruct you as to when to start taking Lixiana.

- *Transitioning from oral anticoagulants of the non-VKA type (for example: dabigatran, rivaroxaban, or apixaban) to Lixiana*
  - Stop the treatment with oral anticoagulants of the non-VKA type (for example: dabigatran, rivaroxaban, or apixaban) and start taking Lixiana at the time of the next scheduled dose.

- *Transitioning from injectable anticoagulants (for example, heparin) to Lixiana*
  - Stop taking the anticoagulant (for example, heparin) and start taking Lixiana at the time of the next scheduled dose.

- *Transitioning from Lixiana to vitamin K antagonists (for example, warfarin)*
  - If you are taking 60 mg of Lixiana - your doctor will instruct you to reduce the dosage of Lixiana to one 30 mg tablet per day and to take it together with the vitamin K antagonist (for example, warfarin). Your doctor will take blood measurements and will instruct you as to when to stop taking Lixiana.
  - If you are taking 30 mg of Lixiana (reduced dosage) - your doctor will instruct you to reduce the dosage of Lixiana to one 15 mg tablet per day and to take it together with the vitamin K antagonist (for example, warfarin). Your doctor will take blood measurements and will instruct you as to when to stop taking Lixiana.

- *Transitioning from Lixiana to oral anticoagulants of the non-VKA type (for example: dabigatran, rivaroxaban, or apixaban)*
  - Stop taking Lixiana and start taking the oral anticoagulant of the non-VKA type (for example: dabigatran, rivaroxaban, or apixaban) at the time of the next scheduled dose of Lixiana.

- *Transitioning from Lixiana to injectable anticoagulants (for example, heparin)*
  - Stop taking Lixiana and start the treatment with the injectable anticoagulant (for example, heparin) at the time of the next scheduled dose of Lixiana.

- **Patients undergoing cardioversion**
  - If you suffer from cardiac arrhythmia and have to undergo cardioversion in order to restore normal, regular heart rhythm, take Lixiana at the times deemed appropriate by the doctor in order to prevent formation of blood clots in the brain and in other blood vessels in your body.

If you have accidentally taken a higher dosage or if a child has accidentally swallowed the medicine, immediately consult a doctor or proceed to a hospital emergency room and bring the medicine package with you.

An overdose of Lixiana may increase the risk of bleeding.

If you forget to take the medicine

If you forget to take the medicine at the scheduled time, take the tablet immediately and continue the following day with the once daily tablet. Do not take a double dose the same day in order to make up for a forgotten dose.

Adhere to the treatment regimen as recommended by the doctor.

Even if there is an improvement in your health condition, do not stop treatment with the medicine without consulting with your doctor.

If you stop taking the medicine

Lixiana treats and prevents severe medical conditions.

Do not stop taking the medicine without consulting your doctor.

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

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

4. <u>Side effects</u>

As with any medicine, the use of Lixiana 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.

As with similar medicines (intended to reduce blood clotting) Lixiana may cause hemorrhages which may be life threatening. In certain cases the hemorrhages may be occult.
Consult a doctor immediately if you experience persistent bleeding or show signs of heavy bleeding (unusual weakness, fatigue, paleness, dizziness, headaches or unexplained puffiness).
Your doctor will decide whether to follow you up more closely or to change the medicine.

Common side effects (effects that occur in 1-10 users out of 100)

- Abdominal pain
- Abnormal liver blood tests
- Cutaneous or subcutaneous bleeding
- Anaemia (low red blood cell counts)
- Nosebleed
- Vaginal bleeding
- Rash
- Intestinal bleeding
- Bleeding from the mouth and/or throat
- Blood in the urine
- Bleeding from an injury (puncture)
- Stomach bleeding
- Dizziness
- Nausea
- Headache
- Itching

Uncommon side effects (effects that occur in 1-10 users out of 1,000)

- Bleeding in the eyes
- Bleeding from a surgical wound after surgery
- Blood in the spit when coughing
- Bleeding in the brain
- Other types of bleeding
- Low blood platelet count (which can affect clotting)
- An allergic reaction
- Hives

Rare side effects (effects that occur in 1-10 users out of 10,000)

- Intramuscular bleeding
- Bleeding in joints
- Bleeding in the abdomen
- Bleeding in the heart
- Intracranial bleeding
- Postsurgical bleeding
- Anaphylactic (allergic) shock
- Swelling of various parts of the body as a result of an allergic reaction

Not known (frequency cannot be estimated from the available data):

- bleeding in the kidney sometimes with presence of blood in urine leading to inability of the kidneys to work properly (anticoagulant-related nephropathy).

If a side effect occurs, 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 "Reporting Side Effects Due to Drug Treatment" on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by clicking on the link: https://sideeffects.health.gov.il/

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of children and/or infants in order to prevent 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) that appears on the package.
The expiry date refers to the last day of that month.

Storage conditions: Below 30°C.

6. FURTHER INFORMATION

In addition to the active ingredient the medicine also contains:
Mannitol, Pregelatinized starch, Crospovidone, Hydroxypropyl cellulose, Magnesium stearate

In the film-coat:
Hypromellose, Talc, Macrogol 8000, Titanium dioxide, Carnauba wax

Iron oxide yellow (Lixiana 15 and 60), Iron oxide red (Lixiana 15 and 30)

What does the medicine look like and what are the contents of the package

Lixiana 15 - A round, orange colored tablet (6.7 mm diameter) debossed with “DSC L15”.

Lixiana 30 - A round, pink colored tablet (8.5 mm diameter) debossed with “DSC L30”.

Lixiana 60 - A round, yellow colored tablet (10.5 mm diameter) debossed with “DSC L60”.

The medicine is packaged in blister packs inside a carton box.

Lixiana 15 - 10 tablets packaged in one tray of 10 tablets.

Lixiana 30 - 28 tablets packaged in 2 trays of 14 tablets each or 30 tablets packaged in 3 trays of 10 tablets each.

Lixiana 60 - 28 tablets packaged in 2 trays of 14 tablets each or 30 tablets packaged in 3 trays of 10 tablets each.

Not all package sizes may be marketed.

Registration holder and address:
Medison Pharma Ltd., Hashiloach 10, POB 7090 Petach Tikva

Manufacturer and address:
Daiichi Sankyo Europe GmbH, Zielstattstrasse 48 81379 Munich Germany

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Lixiana 15 mg: 166-82-36013-00
Lixiana 30 mg: 166-83-36034-00
Lixiana 60 mg: 166-80-36035-00

Revised on September 2023 according to the MOHs guidelines
Lixiana- PIL-0923-V1