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

The medicine is dispensed with a doctor's prescription only

Rivaroxaban S.K. 2.5 mg
Film-coated tablets

Each film-coated tablet contains:
Rivaroxaban 2.5 mg

For information regarding inactive ingredients: see section 2 – "Important information about some of the ingredients of the medicine" and section 6 – "Additional information".

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have additional questions, refer to the doctor or the pharmacist.

Patient safety information card
In addition to the leaflet, the Rivaroxaban S.K. 2.5 mg preparation has a patient safety information card. This card contains important safety information that you must know before starting treatment with Rivaroxaban S.K. 2.5 mg and during the treatment, and act accordingly.
Please review the patient safety information card and the patient leaflet before starting to use the preparation.
You should keep the card for further review, if necessary.

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

1. What is the medicine intended for?

- Rivaroxaban S.K, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel , is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.
- Rivaroxaban S.K,, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events

Therapeutic class: Rivaroxaban S.K. 2.5 mg belongs to a class of medicines called anticoagulants, and acts by reducing the tendency to produce blood clots by blocking a factor involved in the clotting process (factor Xa).

2. Before using the medicine

Do not use this medicine if:

- You are sensitive (allergic) to rivaroxaban or to any of the other ingredients the medicine contains (For information regarding inactive ingredients, see section 2 – "Important information about some of the ingredients of the medicine" and section 6 – "Additional information").
- You suffer from excessive bleeding.
- You have a disease or condition in an organ of the body that increases the risk of serious bleeding (such as: stomach ulcer, injury or bleeding in the brain, recent surgery of the brain or eyes).
- You are taking anticoagulant medications (such as: warfarin, dabigatran, apixaban or heparin), except for cases of switching from treatment with one anticoagulant to another, or while receiving heparin through a venous or arterial line to keep it open.
- You suffer from acute coronary syndrome and have previously experienced bleeding or a blood clot in the brain (stroke).
- You suffer from coronary artery disease or peripheral artery disease and have previously had bleeding in the brain (stroke) or a blockage in the small arteries that provide blood to the deep brain tissue (lacunar stroke) or if you had a blood clot in the brain (ischemic stroke, non- lacunar) within the previous month.
- You suffer from a liver disease which leads to an increased risk of bleeding.
- You are pregnant or breastfeeding.

Do not take Rivaroxaban S.K. 2.5 mg and inform your doctor if any of the above mentioned conditions apply to you.

Special warnings regarding the use of the medicine
Talk to the doctor or pharmacist before taking Rivaroxaban S.K. 2.5 mg.
Do not use Rivaroxaban S.K. 2.5 mg in combination with certain drugs that reduce blood clotting such as prasugrel or ticagrelor, except for acetylsalicylic acid (aspirin) and clopidogrel.

Special caution is required when using Rivaroxaban S.K. 2.5 mg. Before treatment with Rivaroxaban S.K. 2.5 mg, inform the doctor:

- If you are at high risk of bleeding, as could be the case in any of the following situations:
  - Severe kidney disease, since your kidney function might affect the amount of medicine working in your body.
  - You are taking other anticoagulant medications (such as: warfarin, dabigatran, apixaban or heparin), when changing from one anticoagulant to another, or while receiving heparin through a venous or arterial line to keep it open (see below in section 2 – "Drug interactions").
  - You suffer from bleeding disorders.
  - Very high blood pressure, which is not controlled by medicinal treatment.
  - Diseases of the stomach or intestines that might cause bleeding, such as: inflammation of the bowels or stomach, or inflammation of the esophagus, e.g. gastroesophageal reflux disease (a disease in which stomach acid goes upwards into the esophagus) or tumors located in the stomach or bowels or genitals or urinary tract.
  - Problems with the blood vessels of the retina (retinopathy).
  - A lung disease where the bronchi are enlarged and filled with purulent secretions (bronchiectasis), or previous bleeding from your lung.
  - You are over 75 years old.
  - Your body weight is 60 kg or less.
  - You have coronary artery disease with severe symptomatic heart failure.
- If you have a prosthetic heart valve.
- If you know that you have a disease called antiphospholipid syndrome (a disorder of the immune system that causes an increased risk of blood clots), tell your doctor, who will decide whether the treatment should be changed.

If any of the above mentioned conditions apply to you, tell your doctor before you take the medicine. Your doctor will decide whether you should be treated with Rivaroxaban S.K. 2.5 mg and whether you should be kept under close observation.

- If the doctor thinks that you have an increased risk for developing a stomach or intestinal ulcer, he may also give a treatment to prevent it.

If you need to undergo surgery or <u>an invasive procedure</u>

- It is highly important to take Rivaroxaban S.K. 2.5 mg before and after the surgery or invasive procedure at the exact times your doctor has scheduled for you.
- If your surgery involves an intraspinal catheter or injection (e.g., for epidural or spinal anesthesia or for pain relief):
  - It is highly important to take Rivaroxaban S.K. 2.5 mg before and after the injection or the removal of the catheter **at the exact times** your doctor has scheduled for you.
  - Refer to your treating doctor immediately if you experience numbness or weakness in the legs or intestinal problems or bladder problems after the anesthesia wears off, as this requires urgent medical intervention.
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Children and adolescents

The medicine is not intended for use in children and adolescents under the age of 18.

Information regarding the use in children and adolescents is insufficient.

Drug interactions

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

- Certain anti-fungal medicines (such as: fluconazole, itraconazole, voriconazole, posaconazole), except for those only intended for topical application.
- Tablets containing ketoconazole for treatment of Cushing's syndrome – a condition in which the body produces an excess of cortisol.
- Certain medicines for the treatment of bacterial infections (such as: clarithromycin, erythromycin).
- Certain anti-viral medicines for the treatment of human immunodeficiency virus infection (HIV)/AIDS (such as: ritonavir).
- Other anticoagulant medications (such as: enoxaparin, clopidogrel or vitamin K antagonists, such as warfarin and acenocoumarol, prasugrel and ticagrelor [see in section 2 – "Special warnings regarding the use of the medicine"]).
- Anti-inflammatory and analgesic medicines (such as: naproxen or acetylsalicylic acid [aspirin]).
- Dronedarone, a medicine for treatment of irregular heartbeat.
- Certain medicines for treatment of depression (selective serotonin reuptake inhibitors [SSRIs] or serotonin-norepinephrine reuptake inhibitors [SNRIs]).

These medicines may cause increased activity of Rivaroxaban S.K. 2.5 mg. Your doctor will decide whether to treat you with Rivaroxaban S.K. 2.5 mg and whether close medical supervision is required.

Moreover, the doctor or pharmacist should be informed if you are taking:

- Certain medicines for treatment of epilepsy (such as: phenytoin, carbamazepine, phenobarbital).
- St. John's wort (hypericum), a herbal preparation for the treatment of depression.
- Rifampicin (an antibiotic).

These medicines may cause decreased activity of Rivaroxaban S.K. 2.5 mg. Your doctor will decide whether to treat you with Rivaroxaban S.K. 2.5 mg and whether close medical supervision is required.

Use of the medicine and food

Rivaroxaban S.K. 2.5 mg can be taken with or without food.

Pregnancy, breastfeeding and fertility

Do not take Rivaroxaban S.K. 2.5 mg if you are pregnant or breastfeeding.
If there is a chance that you might become pregnant, you must use a reliable contraceptive while taking Rivaroxaban S.K. 2.5 mg.
If you become pregnant while taking the medicine, inform the treating doctor immediately, who will decide how to continue the treatment.

Driving and operating machinery

Rivaroxaban S.K. 2.5 mg may cause dizziness (a common side effect) or fainting (an uncommon side effect) (see section 4 – "side effects"). Do not drive, ride a bicycle, use tools or operate machinery while using Rivaroxaban S.K. 2.5 mg if you experience these symptoms.

Important information about some of the ingredients of the medicine

The medicine contains lactose and sodium.
If you have been told by your doctor that you have an intolerance to certain sugars, speak to your doctor before starting to take Rivaroxaban S.K. 2.5 mg.
The medicine contains less than 1 mmol of sodium (23 mg) per tablet, and is thus considered to be "sodium-free".

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.

- The dosage and treatment regimen will be determined only by the doctor. The generally accepted dosage is:
  One tablet of Rivaroxaban S.K. 2.5 mg twice a day. You should take Rivaroxaban S.K. 2.5 mg at approximately the same times every day (for example, one tablet in the morning and one tablet in the evening).
- Rivaroxaban S.K. 2.5 mg will not be prescribed to you as a single medicine on its own. The doctor will also prescribe one of these medicines:
  - Acetylsalicylic acid known as aspirin, or
  - Acetylsalicylic acid together with clopidogrel.

The doctor will instruct you what dose of the additional medicines you should take (the recommended dose is usually between 75 mg to 100 mg acetylsalicylic acid once a day or a daily dose of 75 mg to 100 mg of acetylsalicylic acid together with a daily dose of 75 mg of clopidogrel).

Do not exceed the recommended dose.

You should start the treatment with Rivaroxaban S.K. 2.5 mg after acute coronary syndrome as soon as possible after stabilization of the acute coronary syndrome, at the earliest 24 hours after hospitalization and when anticoagulant therapy by injection is usually stopped.
Your doctor will instruct you when to start the treatment with Rivaroxaban S.K. 2.5 mg if you are diagnosed with coronary artery disease or with peripheral artery disease.
Your doctor will decide on the duration of treatment.
If you have difficulty swallowing the tablet whole, speak to your doctor about other ways to take Rivaroxaban S.K. 2.5 mg.
The tablet may be crushed and mixed with water or apple puree immediately before it is taken.
If necessary, your doctor will administer crushed Rivaroxaban S.K. 2.5 mg through a feeding tube into your stomach.
No information is available regarding halving/chewing.

If you accidentally take a higher dosage you should refer to your treating doctor immediately. Taking too much Rivaroxaban S.K. 2.5 mg increases your risk for bleeding.
If you took an overdose or if a child accidently swallowed this medicine, go to the doctor or the emergency room of the hospital immediately and take the package of the medicine with you.
Taking the medicine at the same time every day will help you remember to take it.

If you forgot to take the medicine at the required time, do not take a double dose to compensate for a forgotten dose. Take the next dose at the scheduled time and consult a doctor.
Follow the treatment as recommended by the doctor.
Do not stop treatment with the medicine without consulting the doctor.

If you stop taking the medicine this may increase the risk of a stroke or an additional heart attack or death from a disease related to your heart or to your blood vessels.
Do not take medicines in the dark! Check the label and the dose <u>every</u> <u>time</u> you take the medicine. Wear glasses if you need them.
If you have any other questions regarding use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using Rivaroxaban S.K. 2.5 mg may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
Like other similar medicines for reducing the formation of blood clots, Rivaroxaban S.K. 2.5 mg may cause potentially life-threatening bleeding. Heavy bleeding may cause a sudden drop in blood pressure (shock). In certain cases the bleeding may be occult.
Refer to the doctor immediately if you experience any of the following side effects:
Signs of bleeding:
- Cerebral or intracranial bleeding (symptoms may include headache, one- sided weakness, vomiting, convulsions, decreased level of consciousness and neck stiffness. This is a serious medical emergency, seek immediate medical attention!).
- Prolonged or heavy bleeding.
- Abnormal weakness, tiredness, pallor, dizziness, headache, unexplained swelling, shortness of breath, chest pain or angina pectoris.

Your doctor will decide whether to keep you under close observation or change the treatment.
Signs of a severe skin reaction:
- Spreading intense skin rash, blisters or mucosal lesions, e.g. in the mouth or eyes (Toxic Epidermal Necrolysis/Stevens-Johnson syndrome).
- A drug reaction that causes rash, fever, inflammation of internal organs, blood abnormalities and systemic illness (DRESS syndrome).

The frequency of these side effects is very rare (up to one in 10,000 users).
Signs of a severe allergic reaction:
- Swelling of the face, lips, mouth, tongue or throat; difficulty swallowing; hives and breathing difficulties; sudden drop in blood pressure.

The frequencies of severe allergic reactions are very rare (anaphylactic reactions, including anaphylactic shock; may affect up to one in 10,000 users) or uncommon (angioedema and allergic edema; may affect up to one in 100 users).
Additional side effects
Common side effects (effects that may affect up to one in 10 users):
- Reduction in red blood cells which can cause pallor, weakness or breathlessness
- Gastric or intestinal bleeding, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nose bleeding, bleeding in the gums
- Bleeding into the eye (including bleeding from the whites of the eyes)
- Bleeding into tissue or a cavity of the body (local hematoma, bruising)
- Coughing blood
- Bleeding from the skin or under the skin
- Post-operative bleeding
- Oozing of blood or fluid from a surgical wound
- Limb swelling
- Pain in the limbs
- Impaired function of the kidneys (may be seen in tests performed by your doctor)
- Fever
- Abdominal pain, digestive difficulties, nausea or vomiting, constipation, diarrhea
- Low blood pressure (symptoms may be feeling dizzy or fainting when standing up)
- General decrease in strength and energy (weakness, tiredness), headaches, dizziness
- Rash, itching of the skin
- Blood tests may show an increase in some liver enzymes

Uncommon side effects (effects that may affect up to one in 100 users):
- Bleeding into the brain or inside the skull (see above, 'Signs of bleeding')
- Bleeding into a joint causing pain and swelling
- Thrombocytopenia (low number of platelets, which are cells that help blood to clot)
- Allergic reactions, including allergic skin reactions
- Impaired liver function (can be discovered in tests performed by the doctor)
- Blood tests may show an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- Fainting
- General malaise
- Rapid heartbeat
- Dry mouth
- Hives (urticaria)

Rare side effects (effects that can affect up to one in 1,000 users):
- Bleeding into a muscle
- Cholestasis (decreased bile flow), inflammation of the liver (hepatitis), including hepatocellular injury (inflamed liver, including liver injury)
- Yellowing of the skin and the eyes (jaundice)
- Localized swelling
- Local hematoma in the groin as a complication of the cardiac procedure where a catheter is inserted into your leg artery

very rare side effects (effects that may affect up to 1 user in 10,000):
- Accumulation of eosinophils, a type of white granulocytic blood cells that cause lung inflammation (eosinophilic pneumonia).
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Side effects with unknown frequency (frequency cannot be estimated from the available data):
- Kidney failure after a severe bleeding

- Bleeding in the kidney is sometimes accompanied by the presence of blood in the urine leading to the inability of the kidneys to work properly (anticoagulant-related nephropathy)
- Increased pressure within muscles of the legs or arms after bleeding, which leads to pain, swelling, altered sensation, numbness or paralysis (compartment syndrome after bleeding)

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

Reporting side effects

Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.il.

5. How to store the medicine?

- 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 to avoid poisoning. Do not induce vomiting without an explicit instruction from 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.
- **Store below 25°C.**
- Do not throw medicines in the trash. Ask the pharmacist what to do with medicines you no longer use; this way you can protect the environment.

crushed tablets

Crushed tablets are stable in water for up to 4 hours.

6. Additional information

In addition to the active ingredient the medicine also contains:

Lactose, Cellulose microcrystalline, croscarmellose sodium, poloxamer 188, hypermellose, magnesium stearate, sodium lauryl sulfate, titanium dioxide, silica colloidal anhydrous, macrogol 400, yellow iron oxide.

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

Light yellow, round biconvex tablets debossed with "2.5" on one side and plain on the other side.

The tablets come in blister packs in packages of 10,14,20,28,30,56,98,168,196,100 tablets.

Not all package sizes may be marketed.

Name and address of the manufacturer

PHAROS – PHARMACEUTICAL ORIENTED SERVICES SINGLE MEMBER LTD, Greece

LESVOU STREET (END), THESI LOGGOS, INDUSTRIAL ZONE, 14452, METAMORFOSSI ATTIKIS GREECE

Name and address of marketing authorization holder:

K.S.KIM INTERNATIONAL (SK- PHARMA) LTD., ISRAEL

94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139.

The leaflet was revised in May 2023 in accordance with the Ministry of Health guidelines.

Registration number of the medicine in the national drug registry of the Ministry of Health: 173-04-37601

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