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

The medicine is dispensed with a doctor's prescription only

Rivaroxaban Propharm 15 mg
Rivaroxaban Propharm 20 mg
Film-coated tablets

Each tablet contains:
rivaroxaban 15 mg
rivaroxaban 20 mg

Inactive ingredients and allergens in the preparation: see section 6 "Further information" and section 2 under "Important information about some of the ingredients of the medicine".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to your doctor or 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.

In addition to the leaflet, the Rivaroxaban Propharm is provided with a patient safety information card.
This card contains important information that you must know and abide by before starting and during treatment with Rivaroxaban Propharm.
Read the Patient Safety Information Card and the patient leaflet before starting to use the preparation.
Keep the card and leaflet for further reading if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

Rivaroxaban Propharm is intended for adults with the following conditions:

- to prevent blood clots in brain (stroke) and other blood vessels in the body in patients with an irregular heart rhythm called non-valvular atrial fibrillation and with one or more of the following risk factors: congestive heart failure, high blood pressure, age (75 or older), diabetes, prior stroke, or transient ischemic attack.
- to treat blood clots in the veins of the legs (deep vein thrombosis) and in the blood vessels of the lungs (pulmonary embolism) and to prevent the recurrence of blood clots in the blood vessels of the legs and/or lungs.

Rivaroxaban Propharm is intended for children and adolescents below the age of 18 who weigh between 30 kg to 50 kg:

- to treat blood clots in veins (venous thromboembolism) and prevent recurrence of blood clots in the veins or blood vessels of the lungs, following initial treatment of at least 5 days with injectable medicines used to treat blood clots.

Therapeutic group: Rivaroxaban Propharm belongs to a group of medicines called antithrombotic agents and acts by reducing the tendency to form blood clots by blocking a factor involved in the clotting process (Factor Xa).

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to rivaroxaban or to any of the other ingredients contained in the medicine. For the list of inactive ingredients, see section 6 "Further Information".
- you are suffering from excessive bleeding.
- you have a disease or a condition in an organ of the body that increases the risk of serious bleeding (e.g., stomach ulcer, brain injury or bleeding, recent brain or eye surgery).

- you are taking medicines to prevent blood clots (e.g., warfarin, dabigatran, apixaban or heparin), except in cases of switching from one anticoagulant to another, or when you are receiving heparin through a venous or arterial catheter to keep it open.
- you are suffering from a liver disease that increases the risk of bleeding.
- you are pregnant or breastfeeding.

Do not take Rivaroxaban Propharm and tell your doctor if any of the conditions described above applies to you.

Special warnings regarding use of the medicine
Before taking Rivaroxaban Propharm, talk to your doctor or pharmacist.

Special caution is required when using Rivaroxaban Propharm. Before treatment with Rivaroxaban Propharm, tell your doctor:
- if you are at an increased risk of bleeding, as could be the case in any of the following situations:
  - severe kidney disease in adults and moderate to severe kidney disease in children and adolescents, since kidney function may affect the amount of medicine acting in your body. (See section 3 "How should you use the medicine?" regarding the recommended dosage in case of kidney disease).
  - you are taking other medicines to prevent blood clotting (e.g., warfarin, dabigatran, apixaban or heparin), when you are switching from one anticoagulant to another, or when you are receiving heparin through a venous or arterial line to keep it open (see "Drug interactions" in section 2).
  - you suffer from bleeding
  - very high blood pressure, not controlled by medication therapy.
  - a disease of the stomach or bowel that may cause bleeding, e.g., inflammation of the bowels or stomach, or inflammation of the esophagus as a result, for example, of gastroesophageal reflux disease (a disease in which acid from the stomach rises to 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 in which the bronchi are widened and filled with pus (bronchiectasis), or previous bleeding from the lung.
- 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 if the treatment should be changed.
- if your doctor determined that your blood pressure is unstable or a surgical or other treatment to remove a blood clot from your lungs is planned.

If any of the above-mentioned conditions applies to you, tell your doctor before taking the medicine. Your doctor will decide if you should be treated with Rivaroxaban Propharm and if you need close observation.

- If your doctor thinks you are at increased risk of developing a stomach or intestinal ulcer, they may also give you treatment to prevent it.

If you are due to undergo surgery <u>or an invasive procedure</u>
- it is very important that you take Rivaroxaban Propharm before and after the surgery or the invasive procedure, exactly at the times scheduled for you by your doctor.
- If your surgery involves a catheter or injection into your spinal column (e.g., for epidural or spinal anesthesia or pain alleviation):
  - it is very important to take Rivaroxaban Propharm before and after the injection or removal of the catheter, exactly at the times scheduled for you by the your doctor.
  - refer to your doctor immediately if you suffer from numbness or weakness of the legs or from problems with the bowel or bladder after the anesthesia has worn off, since urgent medical intervention is necessary.

Children and adolescents
Rivaroxaban Propharm tablets **are not recommended for children who weigh below 30 kg.**
There is insufficient information about the use in children and adolescents in the adult indications.

Drug Interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell your doctor or pharmacist.
Especially if you are taking:
- certain medicines for fungal infections (e.g., fluconazole, itraconazole, voriconazole, posaconazole), with the exception of those intended for application to the skin only.
- tablets containing ketoconazole to treat Cushing's syndrome – a condition in which the body produces an excess of cortisol.
- certain medicines to treat bacterial infections (e.g., clarithromycin, erythromycin).
- certain antiviral medicines to treat infections of the AIDS virus (HIV) (e.g., ritonavir).
- other anticoagulants (e.g., enoxaparin, clopidogrel or vitamin K antagonists such as warfarin and acenocoumarol).
- anti-inflammatory and pain-relieving medicines (e.g., naproxen or acetylsalicylic acid [aspirin]).
- dronedarone, a medicine to treat irregular heartbeat.
- certain medicines to treat depression (selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).

If any of the above-mentioned conditions applies to you, tell your doctor before taking the medicine. These medicines may lead to increased activity of Rivaroxaban Propharm. Your doctor will decide if you should be treated with Rivaroxaban Propharm and if close medical observation is necessary.

Similarly, inform your doctor or pharmacist if you are taking:
- certain medicines for treatment of epilepsy (e.g., phenytoin, carbamazepine, phenobarbital).
- the herbal preparation for treatment of depression, St. John's wort (Hypericum).
- rifampicin (an antibiotic).

If any of the above-mentioned conditions applies to you, tell your doctor before taking the medicine. These medicines may lead to reduced activity of Rivaroxaban Propharm. Your doctor will decide if you should be treated with Rivaroxaban Propharm and if close medical observation is necessary.

Use of the medicine and food
The medicine must be taken with food and swallowed with water.

Pregnancy, breastfeeding and fertility
Do not take Rivaroxaban Propharm if you are pregnant or breastfeeding.
If there is a chance that you could become pregnant, use a reliable contraceptive while taking Rivaroxaban Propharm.
If you become pregnant while taking the medicine, refer immediately to your doctor, who will decide how to continue treatment.

Driving and use of machines
Rivaroxaban Propharm may cause dizziness (a common side effect) or fainting (an uncommon side effect) (see section 4, "Side effects"). Do not drive, ride a bicycle or use any tools or machines while using Rivaroxaban Propharm if you are affected by these symptoms.

Important information regarding some of the ingredients of the medicine
The medicine contains lactose and sodium.
If you have been told by your doctor that you suffer from an intolerance to certain sugars, refer to your doctor before you start taking Rivaroxaban Propharm.

The medicine contains less than 1 mmol sodium (23 mg) per tablet and is therefore considered essentially “sodium-free”.

3. HOW SHOULD YOU USE THE MEDICINE?

- Always use this preparation according to your doctor’s instructions. Check with your doctor or pharmacist if you are uncertain about the preparation dosage and treatment regimen. The dosage and treatment regimen will be determined by your doctor only.

- **Adults**
  - To prevent blood clots in the brain (stroke) and other blood vessels in the body, the usual dosage is one tablet of 20 mg once a day.

  - If you have poor kidney function, the dose may be reduced to one 15 mg tablet once a day.

  - If you need to undergo a procedure to treat blocked blood vessels in your heart (a procedure called percutaneous coronary intervention - PCI with an insertion of a stent), there is limited information about reducing the dose to one 15 mg tablet of Rivaroxaban Propharm once a day in addition to an antiplatelet medicine such as clopidogrel.

  - To treat blood clots in the veins of your legs and blood clots in the blood vessels of your lungs, and to prevent blood clots from recurring, the usual dose is one 15 mg tablet twice a day for the first 3 weeks and then one 20 mg tablet once a day. After completing at least 6 months of treatment, your doctor may decide to continue treatment with one Rivaroxaban Propharm 10 mg tablet once a day.

  - If you have impaired kidney function and take Rivaroxaban Propharm 20 mg once a day, your doctor may decide to reduce the dose after 3 weeks to one 15 mg tablet once a day if the risk for bleeding is greater than the risk for having another blood clot.

- **Children and adolescents**
  The dose of Rivaroxaban Propharm depends on body weight and will be calculated by your doctor.
  - The recommended dose for children and adolescents who **weigh between 30 kg and less than 50 kg** is one **tablet** of **Rivaroxaban Propharm 15** mg once a day.
  - The recommended dose for children and adolescents **who weigh 50 kg or more** is one **tablet of Rivaroxaban Propharm 20** mg once a day.

Take each dose of Rivaroxaban Propharm with a drink (e.g. water or juice) during a meal. Take the tablets every day at the same time. Please consider setting an alarm to remind you. For parents or caregivers: please observe the child when they take the medicine to ensure the full dose was taken.

As the dose of Rivaroxaban Propharm is based on body weight, it is important to keep scheduled doctor’s visits because the dose may need to be adjusted as weight changes.
Never adjust the dose of Rivaroxaban Propharm by yourself. Your doctor will adjust the dose if necessary.

Do not split the tablet in an attempt to provide part of a tablet dose. If a lower dose is required, use a different medicine containing Rivaroxaban 1 mg/ml in granules to prepare an oral suspension. For children and adolescents who are unable to swallow tablets whole, use a different medicine containing Rivaroxaban 1 mg/ml in granules to prepare an oral suspension. If Rivaroxaban 1 mg/ml granules to prepare the oral suspension is not available, the tablet may be crushed and mixed with water or apple puree immediately before taking. Eat immediately after taking the crushed medicine. If necessary, your doctor will give you crushed Rivaroxaban Propharm through a stomach tube.

Do not exceed the recommended dose.

- Duration of treatment
  Take Rivaroxaban Propharm each day until your doctor tells you to stop.
  Your doctor will decide on the duration of treatment with the medicine

- Form of administration

This medicine must be taken with food, and it is advisable to swallow the tablet with water.
If it is difficult for you to swallow the tablet whole, talk to your doctor about other ways to take Rivaroxaban Propharm.
The tablet may be crushed and mixed with water or apple puree, immediately before taking.
Eat immediately after taking the crushed medicine.
If necessary, your doctor will give you crushed Rivaroxaban Propharm through a stomach tube.
There is no information about splitting/chewing.

Taking the medicine at the same time every day will help you remember to take it.

If you spit up the dose or vomit
- less than 30 minutes after taking Rivaroxaban Propharm, take a new dose.
- more than 30 minutes after taking Rivaroxaban Propharm, **do not** take a new dose. Take the next dose of Rivaroxaban Propharm at the next scheduled time.

Contact your doctor if you repeatedly spit up the dose or vomit after taking Rivaroxaban Propharm.

If you accidentally take too high a dosage, refer to your doctor immediately. Taking too much Rivaroxaban Propharm increases the risk of bleeding.
If you took an overdose, or if a child has accidentally swallowed some medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the required time
Adults, children and adolescents:
- With a dosage of one Rivaroxaban Propharm 15 mg tablet or Rivaroxaban Propharm 20mg tablet **once** a day, take a dose as soon as you remember, but under no circumstances take a double dose or two doses on the same day! Take the next dose on the following day and then continue taking one tablet once a day and consult your doctor.

Adults:
- With a dosage of 15 mg **twice** a day, take a dose as soon as you remember. Do not take more than two 15 mg tablets in a single day. You can take two 15 mg tablets together for a dose of 30 mg in one day. On the following day, you should continue and take one 15 mg tablet twice a day.

Adhere to the treatment regimen as recommended by your doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting your doctor, since Rivaroxaban Propharm treats and prevents serious conditions.

If you stop taking the medicine, you are hurting its therapeutic and preventive ability.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Rivaroxaban Propharm 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.

Like other similar medicines to reduce the formation of blood clots, Rivaroxaban Propharm can cause bleeding, which may be life-threatening. Heavy bleeding may lead to a sudden drop in blood pressure (shock). In some cases, the bleeding may not be obvious.

Refer to your doctor immediately if you or your child suffer from any of the following side effects:

Signs of bleeding:

- brain bleeding or bleeding inside the skull (symptoms can include headache, one-sided weakness, vomiting, seizure, decreased level of consciousness, and neck stiffness. This is a serious medical emergency; seek medical attention immediately!).
- prolonged or excessive bleeding.
- exceptional weakness, tiredness, paleness, dizziness, headache, unexplained swelling, breathlessness, chest pain or angina pectoris.

Your doctor will decide whether close monitoring or a change in treatment is necessary.

Signs of a severe skin reactions:

- spreading intense skin rash, blisters or mucosal lesions, e.g., in the mouth or eyes (Stevens-Johnson syndrome/toxic epidermal necrolysis).
- 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 reactions:

- 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) and uncommon (angioedema and allergic edema; may affect up to one in 100 users).

Additional side effects reported in adults, children and adolescents

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
- bleeding in the stomach or bowel, urogenital bleeding (including blood in the urine and heavy menstrual bleeding), nosebleed, bleeding in the gums
- bleeding into the eye (including bleeding from the white of the eye)
- bleeding into tissue or a cavity of the body (hematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following a surgery
- oozing of blood or fluid from a surgical wound
- swelling of the limbs
- pain in the limbs
- impaired function of the kidneys (can be detected in tests performed by your doctor)
- fever
- abdominal pain, indigestion, nausea or vomiting, constipation, diarrhea
- low blood pressure (symptoms of this may be feeling dizzy or fainting when standing up)
- decreased general strength and energy (weakness, tiredness), headache, dizziness
- rash, itchy skin
- blood tests can indicate an elevation of 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 (a low number of platelets, which are cells that help blood to clot)
- allergic reactions, including allergic skin reactions
- impaired function of the liver (can be detected in tests performed by your doctor)
- blood tests may indicate an increase in bilirubin, certain pancreatic or liver enzymes or the number of platelets
- fainting
- generally feeling unwell

- faster heartbeat
- dry mouth
- hives (urticaria)

Rare side effects (effects that may affect up to one in 1,000 users):
- bleeding into a muscle
- cholestasis (decreased bile flow), hepatitis including hepatocellular injury (inflamed liver including liver injury)
- yellowing of the skin and eyes (jaundice)
- localized swelling
- localized collection of blood (hematoma) in the groin resulting from a complication of a cardiac procedure where a catheter is inserted into a leg artery

Very rare side effects (effects that may affect up to one in 10,000 users):
- accumulation of eosinophils, a type of white granulocytic blood cells that cause inflammation in the lungs (eosinophilic pneumonia)

Side effects of unknown frequency (the frequency cannot be estimated from the available information):
- kidney failure after severe bleeding
- bleeding in the kidney, sometimes accompanied by blood in the urine, leading to 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)

Side effects in children and adolescents
In general, the side effects observed in children and adolescents treated with Rivaroxaban Propharm were similar to those observed in adults and were primarily mild to moderate in severity.

Side effects that were observed more often in children and adolescents:

Very common side effects (effects that may affect more than 1 in 10 users):
- headache
- fever
- nosebleed
- vomiting

Common side effects (effects that may affect up to 1 in 10 users):
- raised heartbeat
- blood tests may show an increase in bilirubin (bile pigment)
- thrombocytopenia (low number of blood platelets which are cells that help blood clot)
- heavy menstrual bleeding

Uncommon side effects (effects that may affect up to 1 in 100 users):
- blood tests may show an increase in a subcategory of bilirubin (direct bilirubin, bile pigment)

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 your 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 safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your 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.
- Do not store the medicine at a temperature above 25°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

- **In addition to the active ingredient, the medicine also contains:**
  Tablet core:
  Cellulose microcrystalline, lactose monohydrate, hypromellose 2910, croscarmellose sodium, magnesium stearate, sodium laurilsulfate.
  Tablet coating:
  Hypromellose 2910, macrogol 3350, titanium dioxide, iron oxide red.

- **What does the medicine look like and what are the contents of the package:**
  Rivaroxaban Propharm 15 mg: round, red, biconvex, film-coated tablets marked with “15” on one side.
  Rivaroxaban Propharm 20 mg: round, dark red, biconvex, film-coated tablets marked with “20” on one side.
  The tablets come in trays (blisters) in packs of 28 tablets.

- **Registration holder and address:** Propharm Ltd., 23 Ben Gurion, Zichron Yaacov.

- **Manufacturer and address:**
  Adalvo Limited, Malta Life Science Park, Building 1, Level 4, Sir Temi Zammit Buildings, San Gwann, Industrial estate, San Gwann, SGN 3000, Malta
- Revised in October 2023 according to MOH guidelines.
- Registration numbers of the medicines in the National Drug Registry of the Ministry of Health:
  Rivaroxaban Propharm 15 mg: 175-29-36752-99
  Rivaroxaban Propharm 20 mg: 175-30-36753-99