PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986
The medicine is dispensed with a doctor's prescription only

Xarelto® 2.5 mg
Film-coated Tablets

Each tablet contains:
Rivaroxaban 2.5 mg

Inactive ingredients and allergens: See section 6 "Further Information" and in section 2 "Important information regarding 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 the doctor or pharmacist.

Patient Safety Information Card
In addition to the leaflet, there is a patient safety information card for Xarelto 2.5 mg preparation. This card contains important safety information that you must know and act upon, before starting and during the course of treatment with Xarelto 2.5 mg. Read the patient safety information card and the patient leaflet before starting to use the preparation. Keep the card for later reference, if needed.

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.

1) WHAT IS THE MEDICINE INTENDED FOR?

Xarelto, in combination with acetylsalicylic acid (known as aspirin), or in combination with acetylsalicylic acid and clopidogrel, is intended to prevent atherothrombotic events in adult patients after acute coronary syndrome (a group of conditions including heart attack and unstable angina, which is a severe type of chest pain), and who have an increase in certain cardiac biomarkers in blood tests.

Xarelto, in combination with acetylsalicylic acid (known as aspirin), is intended to prevent atherothrombotic events in adult patients with coronary artery disease or symptomatic peripheral arterial disease who are at high risk for ischemic events.

Therapeutic group: Xarelto 2.5 mg belongs to a group of medicines called anticoagulants, and acts by reducing the tendency to form blood clots by blocking a factor involved in the blood-clotting process (Factor 10a).

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 clotting (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 have an acute coronary syndrome and have previously experienced bleeding or a blood clot in the brain (stroke).
- you have coronary artery disease or peripheral artery disease and previously had bleeding in your brain (stroke) or there was a blockage of the small arteries providing blood to the brain's deep tissues (lacunar stroke) or if you had a blood clot in your brain (ischemic, non-lacunar stroke) in the previous month.
- you are suffering from a liver disease which leads to an increased risk of bleeding.
- you are pregnant or breastfeeding.

Do not take Xarelto 2.5 mg and tell your doctor if any of the conditions described above apply to you.

Special warnings regarding use of the medicine
Talk to the doctor or pharmacist before taking Xarelto 2.5 mg.
Do not use Xarelto 2.5 mg in combination with certain other medicines which reduce blood clotting, such as prasugrel or ticagrelor, with the exception of acetylsalicylic acid (aspirin) and clopidogrel.

Special caution is required when using Xarelto 2.5 mg
- if you are at high risk of bleeding, as could be the case in any of the following situations:
  - a severe kidney disease, since your kidney function may affect the amount of medicine acting in your body.
  - 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 catheter to keep it open (see "If you are taking, or have recently taken, other medicines..." in section 2).
  - you are suffering from bleeding.
  - very high blood pressure, which is not controlled by medicinal treatment.
  - diseases 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 genital tract 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.
  - you are older than 75 years.
  - you weigh less than 60 kg.
  - if you have a 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 if the treatment may need to be changed.

If any of the above-mentioned conditions apply to you, tell the doctor before taking this medicine. The doctor will decide if you should be treated with Xarelto 2.5 mg and if you need close monitoring.
- If the doctor thinks you are at increased risk of developing a stomach or intestinal ulcer, the doctor may also give you prophylactic treatment.

If you are due to undergo surgery or an invasive procedure
- it is very important to take Xarelto 2.5 mg before and after the surgery or the invasive procedure at the exact times that the doctor determined for you.
- if your operation involves a catheter or injection into your spinal column (e.g., for epidural or spinal anesthesia or pain relief):
  - it is very important to take Xarelto 2.5 mg before and after the injection or removal of the catheter, **exactly at the times** determined for you by the doctor.
  - refer to the attending doctor immediately if you suffer from numbness or weakness of the legs or problems with the bowel or bladder after the anesthesia has worn off, because urgent medical intervention is necessary.

Children and adolescents
The medicine is not intended for children and adolescents under 18 years of age. There is not enough information about the use in children and adolescents.

Drug interactions
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the 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 only for application to the skin.
- 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, prasugrel and ticagrelor [see "Special warnings regarding use of the medicine" in section 2]).
- anti-inflammatory and pain-relieving medicines (e.g., naproxen or acetylsalicylic acid [aspirin]).
- dronedarone, a medicine to treat irregular heartbeat.
- some medicines to treat depression (selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).

These medicines may lead to increased activity of Xarelto 2.5 mg. Your doctor will decide if you should be treated with Xarelto 2.5 mg and if close medical observation is necessary.

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

These medicines may reduce the activity of Xarelto 2.5 mg. Your doctor will decide if you should be treated with Xarelto 2.5 mg and if close medical observation is necessary.

Use of the medicine and food
Xarelto 2.5 mg can be taken with or without food.

Pregnancy, breastfeeding and fertility
Do not take Xarelto 2.5 mg if you are pregnant or breastfeeding.
If there is a chance that you will become pregnant, use a reliable contraceptive while taking Xarelto 2.5 mg.
If you become pregnant while taking the medicine, refer immediately to the doctor, who will decide upon the continuation of treatment.

Driving and use of machines
Xarelto 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 or use any tools or machines while using Xarelto 2.5 mg 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 the doctor that you suffer from an intolerance to certain sugars, refer to the doctor before you start taking Xarelto 2.5 mg.
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 in accordance with the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the preparation dosage and treatment regimen.
- The dosage and treatment regimen will be determined by the doctor only.

The recommended dosage is generally:
One Xarelto 2.5 mg tablet, twice a day. Take Xarelto 2.5 mg at approximately the same times every day (for example, one tablet in the morning and one tablet in the evening).
- Xarelto 2.5 mg will not be given to you on its own. The doctor will instruct you to also take one of the following medicines:
  - acetylsalicylic acid, known as aspirin, or
  - acetylsalicylic acid together with clopidogrel.

The doctor will instruct you which dosage of the other medicines you should take (the recommended dosage is usually between 75 mg and 100 mg acetylsalicylic acid, once a day, or a daily dose of 75 mg to 100 mg acetylsalicylic acid with a daily dose of 75 mg clopidogrel).
Do not exceed the recommended dose.
Treatment with Xarelto 2.5 mg after acute coronary syndrome should be started as soon as possible after stabilization of the acute coronary syndrome is achieved, at the earliest, 24 hours after admission to hospital and at the time when anticoagulation therapy by injection is normally stopped.
Your doctor will instruct you when to start treatment with Xarelto 2.5 mg if you have been diagnosed with coronary artery disease or peripheral artery disease.
Your doctor will decide on the duration of treatment.

If it is hard for you to swallow the tablet whole, talk to your doctor about other ways of taking Xarelto 2.5 mg.
The tablet can be crushed and mixed with water or apple puree immediately before administration.
If necessary, your doctor will give you crushed Xarelto 2.5 mg through a stomach feeding tube.
There is no information about halving/chewing.

If you accidentally took a higher dosage, refer to the attending doctor immediately. Taking too much Xarelto 2.5 mg increases the risk of bleeding.
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.
Taking the medicine at the same time every day will help you remember to take it.

If you forget to take this medicine at the required time, do not take a double dose to compensate for the forgotten dose. Take the next dose at the usual time and consult a doctor.
Adhere to the treatment regimen 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 an additional stroke or heart attack or death from a disease related to your heart or blood vessels.

Do not take medicines in the dark! Check the label and the 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) SIDE EFFECTS

As with any medicine, use of Xarelto 2.5 mg 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, Xarelto 2.5 mg can cause bleeding, which may be life-threatening. Excessive bleeding may lead to a sudden drop in blood pressure (shock). In some cases, the bleeding may not be obvious.

Refer to the doctor immediately if you 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 the treatment is necessary.

Signs of a severe skin reaction:
- 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 1 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 1 user in 10,000) and uncommon (angioedema and allergic edema; may affect up to 1 user in 100).

Additional side effects
Common side effects (effects that may affect up to one user in 10):
- 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 (localized hematoma, bruising)
- coughing up blood
- bleeding from the skin or under the skin
- bleeding following an operation
- 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 the 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 increase in some liver enzymes

Uncommon side effects (effects that may affect up to one user in 100):
- 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 the doctor)
- blood tests may indicate an increase in bilirubin, some pancreatic or liver enzymes or in the number of platelets
- fainting
- general unwell feeling
- faster heartbeat
- dry mouth
- hives (urticaria)

Rare side effects (effects that may affect up to one user in 1,000):
- 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 the leg artery

Very rare side effects (effects that may affect up to one user in 10,000):
- 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 data):
- kidney failure after severe bleeding
- 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 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:
<u>https://sideeffects.health.gov.il</u>

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 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) that appears on the package. The expiry date refers to the last day of that month.
- Do not store above 25°C.

Do not throw away medicines via wastewater or household waste. Ask the pharmacist how to throw away medicines that are no longer in use. These measures will help protect the environment.

6) FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
  Cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose 5 cP, hypromellose 15 cP, magnesium stearate, macrogol 3350, titanium dioxide, sodium lauryl sulfate, ferric oxide yellow.

Each Xarelto 2.5 mg tablet contains 35.7 mg lactose monohydrate.

- What does the medicine look like and what are the contents of the package?
  Round, light-yellow, biconvex, film-coated tablets marked with "BAYER" on one side and "2.5" and a triangle on the other side.
  The tablets come in trays (blisters) in packs of 14, 56, 60, 168 tablets.

Not all pack sizes may be marketed.
- **Registration Holder and Address:** Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 4527702.
- **Manufacturer and Address:** Bayer AG, Leverkusen, Germany or Bayer HealthCare Manufacturing S.r.l., Milan, Italy.
- Revised in March 2023 according to MOH guidelines.
- Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
  151-87-34048-00, 151-87-34048-01, 151-87-34048-02, 151-87-34048-03