



<p>PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986</p> <p>The medicine is dispensed with a doctor's prescription only</p>		
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Each tablet contains:

Rivaroxaban 15 mg

Rivaroxaban 20 mg

Inactive ingredients and allergens in the preparation: 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.

In addition to the leaflet, Xarelto is provided with a Patient Safety Information Card. This card contains important safety information that you must know and abide by before starting and during treatment with Xarelto. 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.

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 is intended for adults in the following conditions:

- Prevention of blood clots in the brain (stroke) and in other blood vessels in the body, in patients suffering from an irregular heart rhythm called non-valvular atrial fibrillation, and from one or more of the following risk factors: heart failure, hypertension, age (75 years or more), diabetes mellitus, stroke or transient ischemic attack in the past.
- 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 the blood vessels of the legs and/or lungs.

Xarelto is intended for children and adolescents aged less than 18 years, weighing 30 kg or more:

- For treatment of blood clots and prevention of blood clot recurrence in the veins or in the blood vessels of the lungs, following initial treatment of at least 5 days with injectable medicines used to treat blood clots.

Therapeutic group: Xarelto belongs to a group of medicines called antithrombotic agents and acts by lowering 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 are suffering from a liver disease that increases the risk of bleeding.
- you are pregnant or breastfeeding.

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

Special warnings regarding use of the medicine

Before taking Xarelto, talk to the doctor or pharmacist.

Special caution is required when using Xarelto. Before treatment with Xarelto, tell the doctor:

- if you are at increased risk of bleeding, as could be the case in any of the following situations:
 - a 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 a 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 catheter, to keep it open (see “If you are taking, or have recently taken, other medicines...” in section 2).
 - you are suffering from bleeding disorders.
 - very high blood pressure, not controlled by medicinal treatment.
 - 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 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.

- 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 the 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 apply to you, tell the doctor before taking this medicine. The doctor will decide if you should be treated with Xarelto and if you need close monitoring.

If the doctor thinks you are at increased risk of developing a stomach or bowel ulcer, the doctor may also give you prophylactic treatment.

If you are due to undergo surgery or an invasive procedure

- it is very important that you take Xarelto before and after the surgery or invasive procedure exactly at the times determined for you by the doctor.

- if your operation involves a catheter or injection into your spinal column (e.g., for epidural or spinal anesthesia or pain reduction):

- it is very important to take Xarelto 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

Xarelto tablets **are not recommended for children weighing less than 30 kg**. There is not enough information on 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 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 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 (HIV) virus (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 abnormal heartbeat.
- certain medicines to treat depression (selective serotonin reuptake inhibitors [SSRIs] or serotonin norepinephrine reuptake inhibitors [SNRIs]).

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

Similarly, inform the doctor or pharmacist if you are taking:

- certain medicines for treatment of epilepsy (e.g., phenytoin, carbamazepine, phenobarbital).
- St. John’s Wort (Hypericum), the herbal preparation for treatment of depression.
- rifampicin (an antibiotic).

If any of the above-mentioned conditions apply to you, tell the doctor before taking the medicine. These medicines may reduce the activity of Xarelto. Your doctor will decide if you should be treated with Xarelto and if close medical observation is necessary.

Use of the medicine and food

You must take the medicine with food and swallow with water.

Pregnancy, breastfeeding and fertility

Do not take Xarelto if you are pregnant or breastfeeding.

If there is a chance that you could become pregnant, use a reliable contraceptive while taking Xarelto.

If you become pregnant while taking the medicine, refer immediately to the doctor, who will decide upon the continuation of the treatment.

Driving and using machines

Xarelto 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 operate machines while using Xarelto 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.

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

• Adults

- To prevent blood clots in the brain (stroke) and in other blood vessels in the body, the usual dosage is generally one 20 mg tablet once a day.
 - If you suffer from impaired kidney function, the dosage may be reduced to one 15 mg tablet once a day.

If you need to undergo a procedure to treat blocked blood vessels in the heart (a procedure called percutaneous coronary intervention – PCI, with insertion of a stent), there is limited information available on reducing the dosage to one tablet of Xarelto 15 mg, once a day, in addition to an antiplatelet medicine, such as: clopidogrel.

- To treat blood clots in the veins of the legs and in the blood vessels of the lungs, and to prevent recurrence of blood clots, the usual dosage is generally 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, the doctor may decide to continue treatment with Xarelto 10 mg, one tablet daily.

If you suffer from impaired kidney function and take Xarelto 20 mg once a day, the doctor may decide to reduce the dosage after 3 weeks to one 15 mg tablet once a day, if the risk of bleeding is greater than the risk of developing another blood clot.

Children and adolescents

The dosage of Xarelto depends on the body weight, and will be calculated by the doctor.

- The recommended dosage for children and adolescents **weighing between 30 kg and less than 50 kg** is one **Xarelto 15 mg tablet** once a day.

- The recommended dosage for children and adolescents **weighing 50 kg or more** is one **Xarelto 20 mg tablet** once a day.

Take a Xarelto dose with a drink (e.g., water or juice) during a meal. Take the tablets every day at a set time. Please consider using an alarm clock to remind you. For parents or caregivers: please observe the child during administration to ensure that the full dose is taken.

As the Xarelto dosage is based on body weight, it is important to keep scheduled doctor’s visits because the dosage may need to be adjusted as the body weight changes.

Never adjust the dosage of Xarelto by yourself. The doctor will adjust the dosage if necessary.

Do not split the tablet in an attempt to provide a fraction of a tablet dose. If a lower dosage is required, use Xarelto 1 mg/ml granules for preparation of oral suspension. For children and adolescents who are unable to swallow tablets whole, use Xarelto 1 mg/ml granules for preparation of oral suspension.

If Xarelto 1 mg/ml granules for preparation of oral suspension is not available, the tablet can be crushed and mixed with water or apple puree immediately before taking it. You should eat immediately after taking the crushed medicine. If necessary, your doctor will give you crushed Xarelto through a stomach feeding tube.

Do not exceed the recommended dose.

Duration of treatment

Take Xarelto every day until the doctor tells you to stop.

The doctor will decide on the duration of treatment with the medicine.

Method of administration

The medicine must be taken with food and it is recommended that the tablet be swallowed with water.

If it is hard for you to swallow the tablet whole, talk to your doctor about other ways of taking Xarelto.

The tablet can be crushed and mixed with water or apple puree immediately before administration.

Eat immediately after taking the crushed medicine.

If necessary, your doctor will give you crushed Xarelto through a stomach feeding tube.

There is no information regarding halving/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

- If less than 30 minutes have passed since you took Xarelto, take a new dose.

- If more than 30 minutes have passed since you took Xarelto, **do not** take a new dose. In this case, take the next Xarelto dose at the next scheduled time.

Contact the doctor if you repeatedly spit up the dose or vomit after taking Xarelto.

If you accidentally took a higher dosage

Refer to the attending doctor immediately. Taking too much Xarelto 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.

If you forget to take this medicine at the required time

Adults, children and adolescents:

- For the dosage of one tablet of Xarelto 15 mg or Xarelto 20 mg **once** a day, take a dose as soon as you remember, but never take a double dose or two doses on the same day! Take the next dose on the following day and then once a day, as usual, and consult the doctor.

Adults:

- For the dosage of one 15 mg tablet **twice** a day, take a dose as soon as you remember. Do not take more than two 15 mg tablets in a single day. Two 15 mg tablets can be taken together to obtain a dosage of 30 mg on one day. On the following day, carry on taking one 15 mg tablet twice a day.

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 since Xarelto treats and prevents serious conditions.

If you stop taking the medicine, you are impairing its therapeutic and preventive capacity.

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 the doctor or pharmacist.

4) SIDE EFFECTS

As with any medicine, use of Xarelto 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 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 or the 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 the treatment is necessary.

Signs of 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 1 user in 10,000).

Signs of 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 1 user in 10,000) and uncommon (angioedema and allergic edema; may affect up to 1 user in 100).

Additional side effects reported in adults, children and adolescents

Common side effects (effects that may affect up to 1 user in 10):

- reduction in red blood cells which can cause paleness, 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 1 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 1 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 internal 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

- bleeding in the kidney sometimes with presence of blood in 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 Xarelto were similar to those observed in adults and were primarily mild to moderate in their severity.

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

Very common side effects (effects that may affect more than 1 user in 10):

- headache

- fever

- nose bleeding

- vomiting

Common side effects (effects that may affect up to 1 user in 10):

- raised heartbeat

- blood tests can indicate an increase in bilirubin (bile pigment)

- thrombocytopenia (low number of platelets which are cells that help blood to clot)

- heavy menstrual bleeding

Uncommon side effects (effects that may affect up to 1 user in 100):

- blood tests can indicate 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 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 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.

- Store the medicine at a temperature below 30°C.

Crushed tablets

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

- Do not discard medicines in the wastewater or household waste. Ask the pharmacist how to dispose of 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:

Cellulose microcrystalline, lactose monohydrate, croscarmellose sodium, hypromellose 5 cP, hypromellose 15 cP, magnesium stearate, sodium laurylsulfate, macrogol 3350, titanium dioxide, ferric oxide red.

Each Xarelto 15 mg tablet