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

The medicine is dispensed with a doctor's prescription only

Crusia

Solution for injection in a pre-filled syringe with a safety system
20 mg/0.2 ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml, 100 mg/1.0 ml

Crusia Forte

Solution for injection in a pre-filled syringe with a safety system
120 mg/0.8 ml, 150 mg/1.0 ml

Active ingredient and its quantity:
Each syringe of **Crusia** respectively contains:
Enoxaparin Sodium 20 mg, 40 mg, 60 mg, 80 mg or 100 mg
Each syringe of **Crusia Forte** respectively contains:
Enoxaparin Sodium 120 mg or 150 mg
For a list of inactive ingredients, please see section 6.

Read the entire leaflet carefully before using the medicine. Keep this leaflet, you may need to read it again. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.
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.
If a side effect worsens or if a side effect that is not mentioned in this leaflet appears, refer to the doctor or pharmacist.
Crusia/Crusia Forte is a biosimilar preparation. For additional information about biosimilar preparations refer to the Ministry of Health website:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/Registration/Pages/Biosimilars.aspx
Please note, every time you collect the medicine at the pharmacy, it is important that you make sure you get the same medicine your attending specialist doctor prescribed for you. If the medicine you received looks different from the one you usually receive, or the directions for use have been changed, immediately refer to the pharmacist in order to confirm that you have been supplied with the correct medicine. Any switch or change in the dosage of a medicine containing enoxaparin sodium must be conducted by the attending specialist doctor only. Please check that the trade name of the medicine prescribed for you by the specialist doctor, is identical to the name of the medicine that you received from the pharmacist.

1. What is the medicine intended for?

This medicine is given to adults for:
- Prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopedic or general surgery, including cancer surgery.
- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility, at increased risk of venous thromboembolism.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Prevention of thrombus formation in extracorporeal circulation during hemodialysis.
- Acute coronary syndrome:
  - Treatment of unstable angina and non ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
  - Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

Therapeutic class: An anticoagulant belonging to the low molecular weight heparin group.

2. Before using the medicine:

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (enoxaparin sodium) or to any of the other ingredients this medicine contains (see section 6 "Additional information"). Signs of allergy include: rash, problems swallowing or breathing, swelling of the lips, face, throat, tongue or eyes.
- You are allergic to heparin or to other low molecular weight heparin preparations, such as nadroparin, tinzaparin or dalteparin.
- You have had a reaction to heparin that caused a severe decrease in the number of platelets – this reaction is called heparin-induced thrombocytopenia – within the last 100 days or if you have antibodies against enoxaparin in your blood.
- You suffer from heavy bleeding or have a high risk of bleeding (such as in the case of a stomach ulcer, if you have recently had brain or eye surgery), including recent hemorrhagic stroke.
- You are using this medicine to treat blood clots, and are about to undergo spinal or epidural anesthesia or lumbar puncture within 24 hours.

Special warnings regarding the use of the medicine

Before treatment with this medicine, inform the doctor if:
- You have ever had a reaction to heparin that caused a severe decrease in the number of platelets.
- You are about to undergo spinal or epidural anesthesia or lumbar puncture (see the section "Surgeries and anesthetics"): make sure there is waiting time between the use of this medicine and these procedures.
- You have had a heart valve replacement.
- You suffer from an infection of the inner lining of the heart (endocarditis).
- You have a history of stomach ulcers.
- You have had a stroke recently.
- You have high blood pressure.
- You have diabetes or problems with blood vessels in the eye caused by diabetes (diabetic retinopathy).
- You have recently had surgery on your eyes or brain.
- You are elderly (over 65 years old), and especially if you are over 75 years old.
- You have kidney problems.
- You have liver problems.
- You are underweight or overweight.
- You have high blood potassium level (this can be checked with a blood test).
- You are currently using medicines which affect bleeding (see below in the section "Drug interactions").
- You have a problem in the spine or you have had a surgery in the spinal canal.

Children and adolescents

The safety and efficacy of this medicine has not been evaluated in children and adolescents.

Tests and follow-up

You may be requested to have a blood test before starting to use this medicine and at certain intervals while using this medicine, in order to check the levels of platelets and potassium in your blood.

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:
- Warfarin – used for thinning the blood.
- Aspirin (also known as acetylsalicylic acid), clopidogrel or other medicines used to stop the formation of blood clots (see also in section 3 "Changing anticoagulant treatment").
- Dextran injection – used as a blood substitute.
- Ibuprofen, diclofenac, ketorolac or other medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) which are used to treat pain and swelling in arthritis and other conditions.
- Prednisolone, dexamethasone or other medicines used to treat asthma, rheumatoid arthritis and other conditions.
- Medicines which increase the level of potassium in the blood, such as potassium salts, diuretics, certain medicines for heart problems.

Surgeries and anesthetics

If you are about to undergo a lumbar puncture or surgery where an epidural or spinal anesthetic is used, tell your doctor that you are using this medicine (see the section "Do not use the medicine if"). Also, tell your doctor if you have any problems with your spine or if you ever had spinal surgery.

Pregnancy, breastfeeding and fertility

If you are pregnant, think you might be pregnant or are planning to become pregnant, consult your doctor before using this medicine.
If you are pregnant and have a mechanical heart valve, you may be at an increased risk of developing blood clots.
Your doctor will discuss this with you.
If you are breastfeeding or are planning to breastfeed, you should consult your doctor before using this medicine.

Driving and operating machinery

This medicine does not affect the ability to drive and operate machinery.

Important information about some of the ingredients of the medicine

This medicine contains less than 23 mg sodium per dose, therefore the medicine is considered "sodium-free".

3. How should you use the medicine?

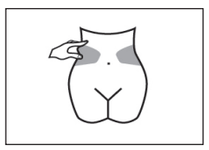
Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the medicine.
The dosage and treatment regimen will be determined only by the doctor.
The dosage depends on the reason for which you are using this medicine.
If you suffer from kidney problems you may need a lower dosage of this medicine.
Do not exceed the recommended dose.
Using the medicine
- When you are at the hospital, usually the doctor or nurse will give you the medicine, because it is given as an injection.
- When you go home you may need to continue to inject this medicine by yourself (see below in the section "Instructions on how to use the syringe – Instructions on self-injecting this medicine").
- This medicine is usually given by a subcutaneous injection.
- This medicine can be given by intravenous injection after certain types of surgery or heart attack.
- This medicine can be added to the tube leaving the body (arterial line) at the start of the dialysis treatment.
- Do not inject this medicine into a muscle.

Instructions on how to use the syringe

How to self-inject this medicine:
If you are able to self-inject this medicine, the doctor or nurse will show you how to do this. Do not try to inject yourself if you have not been instructed how to do so. If you are not sure what to do, talk to the doctor or nurse immediately.
Proper injection under the skin (called "subcutaneous injection") will help reduce pain and bruising at the injection site.
Before self-injecting this medicine:
- Gather the items you need: syringe, alcohol swab or soap and water and sharps disposal container.
- Check the expiry date of the medicine. Do not use after that date.
- Check that the syringe is not damaged and that the solution is clear. If not, use another syringe.
- Make sure that you know the amount of medicine you are going to inject.
- Check your abdomen in order to see if the last injection caused any redness, change in skin color, swelling, oozing or if the injection site is still painful. If so, talk to the doctor or nurse.

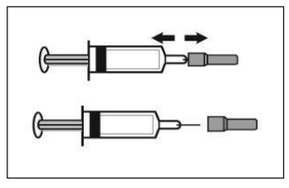
Instructions on self-injecting this medicine:

Preparing the injection site
1. Choose an area on the right or left side of your abdomen. The chosen area should be at least 5 cm away from your belly button towards the body sides.
   - Do not inject yourself at a distance less than 5 cm from the belly button or around existing scars or bruises.
   - Change the place where you inject between the right and left side of the abdomen, depending on the area you last injected.



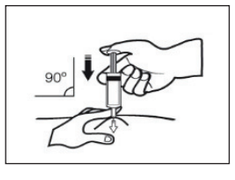
2. Wash your hands. Cleanse (do not rub) the area that you will inject with an alcohol swab or soap and water.
3. Sit or lie in a comfortable position so you are relaxed. Make sure you can see the place you are going to inject. A comfortable chair, a recliner chair, or a bed propped up with pillows, will provide the best position.

Preparing the dose
1. Carefully remove the needle cap from the syringe. Throw away the cap.
   - Do not press on the plunger before injecting yourself in order to eject air bubbles. This action may lead to a loss of the medicine.
   - After you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).

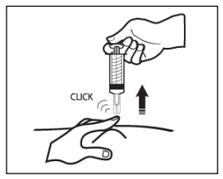


2. When the amount of medicine in the syringe matches your prescribed dose, there is no need to adjust the dose. You are now ready to inject.
3. When the dose depends on your body weight, you may need to adjust the dose in the syringe to match your prescribed dose. In that case, you can get rid of the extra medicine by holding the syringe pointing down (in order to keep the air bubble in the syringe) and ejecting the extra amount into a container.
4. A drop may appear at the tip of the needle. In this case, remove the drop before injecting by tapping on the syringe while the needle is pointing down. You are now ready to inject.

Injecting
1. Hold the syringe in the hand you write with (like a pencil). With the other hand, gently pinch the clean area of the abdomen between the forefinger and thumb to make a fold in the skin.
   - Make sure you hold the skin fold throughout the injection.
2. Hold the syringe so that the needle is pointing down (vertically at an angle of 90 degrees). Insert the full length of the needle into the skin fold.



3. Press down on the plunger with the thumb. This way the medicine will enter the fatty tissue of the abdomen. Complete the injection using all the medicine in the syringe.
4. Remove the needle from the injection site by pulling the syringe straight out while keeping the finger on the plunger rod. Orient the needle away from the user and anyone else in the area. The safety system is activated by pressing strongly on the plunger rod. The protective sleeve will automatically cover the needle and will make an audible "click" which confirms the activation of the safety cap. You can now release the skin fold.



After injecting
1. In order to avoid bruising, do not rub the injection site after you have injected yourself.
2. Throw the used syringe in a sharps disposal container. Close the container lid tightly and place the container out of children's reach. When the container is full, dispose of it as instructed by the doctor or pharmacist.

If you think that the dose is either too strong (for example, you experience unexpected bleeding) or too weak (for example, the dose doesn't seem to be working), talk to the doctor or pharmacist.

Changing anticoagulant treatment

- *Changing from this medicine to blood thinners that are called vitamin K antagonists (such as warfarin)*
  Your doctor will ask you to have blood tests called INR and will tell you when to stop using this medicine according to the results.
- *Changing from blood thinners called vitamin K antagonists (such as warfarin) to this medicine*
  Stop using the vitamin K antagonists. Your doctor will ask you to have blood tests called INR and will tell you when to start using this medicine according to the results.
- *Changing from this medicine to treatment with direct oral anticoagulant*
  Stop using this medicine. Start taking the direct oral anticoagulant 0-2 hours before the time you would have had the next injection of this medicine, then continue as usual.
- *Changing from direct oral anticoagulant to this medicine*
  Stop taking the direct oral anticoagulant. Do not start treatment with this medicine less than 12 hours after the final dose of the direct oral anticoagulant.

If you have accidentally injected a higher dosage than required

If you think that you have used too much or too little of this medicine, immediately consult your doctor, nurse or pharmacist, even if you do not experience unusual effects. If a child has accidentally injected or swallowed this medicine, immediately refer to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forget to use this medicine

If you forget to self-inject a dose, inject it as soon as you remember. Do not self-inject a double dose on the same day in order to compensate for a forgotten dose. Keeping a diary will help you to make sure that you do not forget a dose.

If you stop using this medicine

Follow the treatment as recommended by the doctor. It is important to keep taking injections of this medicine until the doctor decides to stop them. If you stop using them, you could develop a blood clot which can be very dangerous.
Do not take medicines in the dark! Check the label and the dose every time you take the medicine. Wear glasses if you need them.
If you have any other questions regarding the use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using this medicine 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.
Severe side effects:
Stop using the medicine and immediately refer to the doctor or nurse if you have symptoms of a severe allergic reaction (such as rash, difficulty swallowing or breathing, swelling of the lips, face, throat, tongue or eyes).
Stop using the medicine and immediately seek medical treatment if you notice one or more of the following symptoms:
Red, scaly and extensive rash with bumps under the skin and blisters, accompanied by fever. The symptoms usually appear at the begining of treatment (AGEP – acute generelised exanthematous pustulosis).
As with other similar medicines (medicines to reduce blood clotting), the use of this medicine may cause bleeding which could be life-threatening. In some cases, the bleeding cannot be seen.
Immediately talk to the doctor if you experience any bleeding event that doesn't stop by itself or if you have symptoms of excessive bleeding (abnormal weakness, tiredness, pallor, dizziness, headache or unexplained swelling).
Your doctor may decide to keep you under closer observation or change your medicine.
Immediately tell your doctor if:
- You have any sign of blockage of a blood vessel by a blood clot, such as:
  - Pain due to cramping, redness, warmth or swelling in one of the legs – these are symptoms of deep vein thrombosis.
  - Shortness of breath, chest pain, fainting or coughing blood – these are symptoms of a pulmonary embolism.
  - You have a painful rash in the shape of dark red spots under the skin, which do not disappear when you put pressure on them.

Your doctor may ask you to have a blood test in order to check your platelet count.
Additional side effects:
Very common side effects (side effects that occur in more than 1 out of 10 users):
- Bleeding.
- Increased liver enzymes.

Common side effects (side effects that occur in 1-10 out of 100 users):
- You bruise more easily than usual. This could happen because of a blood problem with low platelet count.
- Pink patches on your skin. These are more likely to appear at the injection site of this medicine.
- Skin rash (hives, urticaria).
- Itchy red skin.
- Bruising or pain at the injection site.
- Decrease in red blood cell count.
- High blood platelet count.
- Headache.

Uncommon side effects (side effects that occur in 1-10 out of 1,000 users):
- Sudden severe headache. This may be a sign of bleeding in the brain.
- Tenderness and swelling in the stomach. You may have bleeding in the stomach.
- Large red irregularly shaped skin lesions, with or without blisters.
- Skin irritation (local irritation).
- You notice yellowing of your skin or eyes and your urine becomes darker. This may indicate a liver problem.

Rare side effects (side effects that occur in 1-10 out of 10,000 users):
- Severe allergic reaction. Signs include: rash, problems swallowing or breathing, swelling of the lips, face, throat or tongue.
- An increase in blood potassium levels. This effect is more likely to happen in people with kidney problems or diabetes. Your doctor can check this by performing a blood test.
- An increase in the number of eosinophils in your blood. Your doctor can check this by performing a blood test.
- Hair loss.
- Osteoporosis (a condition where your bones are more likely to break) after long-term use.
- Tingling, numbness and muscular weakness (particularly in the lower part of the body) when you have had a lumbar puncture or a spinal anesthetic.
- Loss of control over your bladder or bowel (so you cannot control when you go to the toilet).
- Hard mass or lump at the injection site.

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 and the syringe. The expiry date refers to the last day of that month.
- Store below 25°C. Do not freeze.
- Do not use the medicine if the syringe is damaged or if the solution is not clear.
- **Crusia/Crusia Forte** pre-filled syringes are intended for single use. Discard any leftover solution that has not been used.
- Do not discard medicines via waste water or the trash. Ask the pharmacist how to dispose of medicines no longer in use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient the medicine also contains:
Water for injections

What does the medicine look like and what are the contents of the package:
Crusia/Crusia Forte is a clear, colorless to pale yellow solution, in a pre-filled syringe with a needle and protective cap.
Crusia 20 mg/0.2 ml: Each package contains 2, 6, 10, 20 or 50 syringes.
Crusia 40 mg/0.4 ml: Each package contains 2, 6, 10, 20, 30 or 50 syringes.
Crusia 60 mg/0.6 ml: Each package contains 2, 6, 10, 12, 24 or 30 syringes.
Crusia 80 mg/0.8 ml: Each package contains 2, 6, 10, 12, 24 or 30 syringes.
Crusia 100 mg/1.0 ml: Each package contains 2, 6, 10, 12, 24 or 30 syringes.
Crusia Forte 120 mg/0.8 ml: Each package contains 10, 30 or 50 syringes.
Crusia Forte 150 mg/1.0 ml: Each package contains 10, 30 or 50 syringes.
Not all package sizes may be marketed.

Marketing authorization holder and address: Tzamal Bio-Pharma Ltd., 20 Hamagshimim St., Petach Tikva.

Manufacturer and address: ROVI Pharma Industrial Services S.A., Madrid, Spain.

Registration number of the medicine in the national drug registry of the Ministry of Health:
Crusia: 162-88-35673
Crusia Forte: 173-13-37520
The leaflet was revised in May 2023 in accordance with the Ministry of Health guidelines.

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