Patient package insert in accordance with the pharmacists' regulations (preparations)-1986
This medicine can be sold with a doctor's prescription only

Crusia

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
Pre-filled syringe

Active ingredient and its quantity:
Each pre-filled syringe with safety device system contains:
Enoxaparin Sodium 20 mg, 40 mg, 60 mg, 80 mg or 100 mg

For a list of inactive ingredients- please see section 6.

Read this entire leaflet carefully before you start using the medicine. This leaflet contains concise information about the medicine. If you have any further questions, refer to your doctor or pharmacist.
This medicine has been prescribed for your treatment. Do not pass it on to others. It might harm them, even if you think that their medical condition is similar to yours.

Please note, every time you collect your medicine at the pharmacy, it is important that you make sure that you always receive the same medicine your attending medical specialist prescribed for you. If the medicine you received appears different from the one you usually receive or the directions for use have changed, please refer to the pharmacist immediately to make sure you have received the correct medicine. Any switch or change in the dosage of a medicine containing enoxaparin sodium must be conducted by the attending medical specialist only. Please check that the trade name of the medicine prescribed by your medical specialist is identical to the name of the medicine that you received from the pharmacist.

1. What is the medicine intended for?

Crusia is indicated in adults for:
- prophylaxis of venous thromboembolic disease in moderate and high risk surgical patients, in particular those undergoing orthopaedic 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 blood clots formation in extra corporeal circulation during haemodialysis.
- 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 group: An anti-coagulant from the low molecular weight heparin group.

2. Before using the medicine:

Do not use the medicine if:

- you are hypersensitive (allergic) to the active ingredient (enoxaparin sodium) or to any of the other ingredients this medicine contains (see section 6 "Additional information"). Signs of an allergic reaction include: rash, swallowing or breathing problems, swelling of the lips, face, throat or tongue.
- you are allergic to heparin or other low molecular weight heparin products 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 eyes surgery), including recent hemorrhagic stroke.
- you are using Crusia to treat blood clots, and are about to receive spinal or epidural anaesthesia or lumbar puncture within 24 hours.

Special warnings regarding the use of the medicine

Before treatment with Crusia, tell the doctor if:
- you have ever had a reaction to heparin that caused a decrease in the number of platelets
- you are about to receive spinal or epidural anesthesia or lumbar puncture (see below Surgeries and Anesthetics): a delay should be respected between Crusia use 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 gastric ulcer
- 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 (called diabetic retinopathy)
- you have had surgery on your eyes or brain recently
- you 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 may be checked with a blood test)
- you are currently using medicines which affect bleeding (see below section "Drug interactions")

Children and adolescents

The safety and efficacy of Crusia has not been evaluated in children or 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, 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 drugs and nutrition supplements, tell the doctor or pharmacist. Especially if you are taking:
- Warfarin - used for thinning the blood
- Aspirin (also known as acetylsalicylic acid or ASA), clopidogrel or other medicines used to stop blood clots from forming (see also in section 3, "Changing anticoagulant treatment")
- Dextran injection - used as a blood replacer
- Ibuprofen, diclofenac, ketorolac or other medicines known as non-steroidal anti-inflammatory agents 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 potassium level in your blood such as potassium salts, diuretics, some medicines for heart problems

Surgeries and Anesthetics
If you are going to have a spinal puncture or an operation where an epidural or spinal anesthetic is used, tell you doctor that you are using Crusia. See "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 may be pregnant or are planning to conceive, consult your doctor or pharmacist 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 should discuss this with you.
If you are breastfeeding or planning to breastfeed, you should consult your doctor before using this medicine.

Driving and use of machinery

Crusia does not affect the ability to drive and operate machinery.

Important information about some of the ingredients of this medicine

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

3. How to use this medicine

Always use according to the doctor's instructions. Check with your doctor or pharmacist if you are not sure.
The dosage and treatment regimen will be determined by the doctor only.
The dosage depends on the reason for which you are using Crusia.
If you suffer from kidney problems you may need a lower dosage of Crusia.

Do not exceed the recommended dose.

Using the medicne
- Usually, your 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 Crusia by yourself (see below "Instructions on how to use the syringe- Instructions on injecting Crusia to yourself:").
- Crusia is usually given by a subcutaneous injection (underneath the skin).
- Crusia can be given by injection into the vein (intravenous) after certain types of surgery or heart attack.
- Crusia can be added to the tube leaving the body (arterial line) at the start of the dialysis session.

Do not inject Crusia into a muscle.

Instructions on how to use the syringe

How to inject Crusia to yourself
If you are able to inject Crusia to yourself with, your 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 your doctor or nurse immediately. Proper subcutaneous injection (under the skin) will help reduce pain and bruising at the injection site.

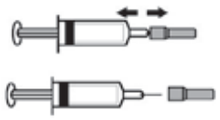
Before injecting Crusia to yourself:
- Gather the items you need: syringe, alcohol swab or soap and water and sharps container.
- Check the expiry date of the medicine. Do not use after that date.
- Check that the syringe is not damaged and the solution is clear. If not, use another syringe.
- Make sure you know the amount of medicine you are going to inject.
- Check your abdomen to see if the last injection caused any redness, change in skin color, swelling, oozing or is still painful. If so talk to your doctor or nurse.

Instructions on injecting Crusia to yourself:

Preparing the injection site
1. Choose an area on the right or left side of your stomach. The chosen area should be at least 5 centimetres away from your belly button and out towards your sides.
- Do not inject yourself at a distance smaller than 5cm from your belly button or around existing scars or bruises.
- Change the place where you inject between the left and right sides of your stomach, 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 lounge chair, recliner, or bed propped up with pillows will provide the ideal position.

Preparing the dose
1. Carefully pull off the needle cap from the syringe. Throw away the cap.
- Do not press on the plunger before injecting yourself to eject air bubbles. This can lead to a loss of the medicine.
- Once 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 medication 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 the prescribed dose. In that case, you can get rid of the extra medicine by holding the syringe pointing down (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. If this occurs, remove the drop before injecting by tapping on the syringe with the needle pointing down. You are now ready to inject.

Injecting
1. Hold the syringe in the hand you write with (like a pencil). With your other hand, gently pinch the cleaned area of your stomach between your 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 straight down (vertically at a 90° angle). Insert the full length of the needle into the skin fold.

3. Press down on the plunger with your thumb. This will insert medicine into the fatty tissue of the stomach. Complete the injection using all of the medicine in the syringe.
4. Remove the needle from the injection site by pulling the syringe straight out while keeping your finger on the plunger rod. Orient the needle away from the user and anyone else who is present. The safety system is activated by pressing firmly on the plunger rod. The protective sleeve will automatically cover the needle and will produce an audible "click" which confirms the activation safety cap. You can now let go of the skin fold.

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

If you think that the dose is either too strong (for example, you are experiencing 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 Crusia to blood thinners called vitamin-K antagonists (e.g. warfarin)*
  Your doctor will request you perform blood tests called INR and tell you when to stop using Crusia accordingly.
- *Changing from blood thinners called vitamin-K antagonists (e.g. warfarin) to Crusia*
  Stop using the vitamin-K antagonist. Your doctor will request you perform blood tests called INR and tell you when to start using Crusia accordingly.
- *Changing from Crusia to treatment with direct oral anticoagulant*
  Stop using Crusia. Start taking the direct oral anticoagulant 0-2 hours before the time you would have had the next Crusia injection, then continue as normal.
- *Changing from treatment with direct oral anticoagulant to Crusia*
  Stop taking the direct oral anticoagulant. Do not start treatment with Crusia less than 12 hours after the final dose of the direct oral anticoagulant.

If you have accedently injected a higher dosage than required

If you think you have used too much or too little Crusia, or if a child accidentally injected or swallowed Crusia, refer to a doctor or to a hospital emergency room immediately and bring the package of the medicine with you.

If you forgot to use Crusia

If you forget to inject a dose to yourself, inject it as soon as you remember. Do not give yourself a double dose on the same day to make up for a forgotten dose. Keeping a diary will help to make sure you do not forget a dose.

If you stop using Crusia

Continue with the treatment as recommended by the doctor.
It is important for you to keep having Crusia injections until the doctor decides to stop them. If you stop, you could develop a blood clot which can be very dangerous.

Do not inject medicines in the dark! Check the label and the dose each time you inject 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 Crusia 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 (medicines to reduce blood clotting), Crusia may cause bleeding which may potentially be life-threatening. In some cases, the bleeding may not be obvious.

If you experience any bleeding event that does not stop by itself or if you experience signs of excessive bleeding (exceptional weakness, tiredness, paleness, dizziness, headache or unexplained swelling), consult your doctor immediately.
Your doctor may decide to keep you under closer observation or change your medicine.

Stop using Crusia and refer to the doctor immediately if you develop any signs of a severe allergic reaction (such as difficulty in breathing, swelling of the lips, mouth, throat or eyes).

You should tell your doctor immediately
- If you have any sign of blockage of a blood vessel by a blood clot such as:
  - cramping pain, redness, warmth, or swelling in one of your legs – these are symptoms of deep vein thrombosis.
  - breathlessness, chest pain, fainting or coughing up blood – these are symptoms of a pulmonary embolism.
  - If you have a painful rash of dark red spots under the skin, which do not go away when you put pressure on them.

Your doctor may request you perform a blood test to check your platelet count.

Very common side effects (occurring in more than 1 in 10 users):
- Bleeding.
- Increase in liver enzymes.

Common side effects (occurring in 1-10 in 100 users):
- You bruise more easily than usual. This could be because of a blood problem with low platelet counts.
- Pink patches on your skin. These are more likely to appear in the area you have been injected with Crusia.
- Skin rash (hives, urticaria).
- Itchy red skin.
- Bruising or pain at the injection site.
- Decreased red blood cell count.
- High platelet counts in the blood.
- Headache.

Uncommon side effects (occurring in 1-10 in 1,000 users):
- Sudden severe headache. This could be a sign of bleeding in the brain.
- A feeling of tenderness and swelling in your stomach. You may have bleeding in your 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 in colour. This could indicate a liver problem.

Rare side effects (occurring in 1-10 in 10,000 users):
- Severe allergic reaction. The signs include: a rash, swallowing or breathing problems, swelling of the lips, face, throat or tongue.
- An increase in blood potassium levels. This is more likely to happen in people with kidney problems or diabetes. Your doctor will be able to check this by carrying out a blood test.
- An increase in blood eosinophil number. Your doctor will be able to check this by carrying out 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 your body) when you have had a spinal puncture or a spinal anaesthetic.
- 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 appears, if one of the side effects worsens or if you suffer from any side effect not listed in this leaflet, consult the doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il), which refers to an online form for reporting side effects, or via the following 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 closed place out of the sight and reach of children and/or infants to avoid poisoning. Do not induce vomiting unless clearly indicated by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears 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 the solution is not clear.
- Crusia prefilled syringes are intended for single use. Any waste or unused solution should be discarded.
- Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. Additional information

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

What the medicine looks like and contents of the pack:
Crusia 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 pack contains 2, 6, 10, 20 or 50 syringes.
Crusia 40 mg/0.4 ml: each pack contains 2, 6, 10, 20, 30 or 50 syringes.
Crusia 60 mg/0.6 ml: each pack contains 2, 6, 10, 12, 24 or 30 syringes.
Crusia 80 mg/0.8 ml: each pack contains 2, 6, 10, 12, 24 or 30 syringes.
Crusia 100 mg/1.0 ml: each pack contains 2, 6, 10, 12, 24 or 30 syringes.
Not all pack sizes may be marketed.

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

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

Drug registration number at the national medicines registry of the Ministry of Health: 162-88-35673

This leaflet was checked and approved by the Ministry of Health in February 2020.

Crusia 20, 40, 60, 80, 100 mg, PIL PB0220-03