PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

PROPRIETARY NAMES, STRENGTHS AND PHARMACEUTICAL FORM:

Zarzio® 30 MU, (300 µg)/ 0,5 mL (Solution for injection or infusion)

Zarzio® 48 MU, (480 µg)/ 0,5 mL (Solution for injection or infusion)

Read all of this leaflet carefully before you are given ZARZIO:

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or your pharmacist.
- ZARZIO has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

1. WHAT ZARZIO CONTAINS:

Active ingredient:

ZARZIO 30 MU: Each pre-filled syringe contains 30 million units (MU) / 300 µg filgrastim per 0,5 mL.

ZARZIO 48 MU: Each pre-filled syringe contains 48 million units (MU) / 480 µg filgrastim per 0,5 mL.

Inactive ingredients:

Glutamic acid, polysorbate 80, sorbitol and water for injection.

Contains sorbitol (25,00 mg per 0,5 mL syringe).

2. WHAT ZARZIO IS USED FOR:

ZARZIO is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of proteins called cytokines. ZARZIO stimulates the bone marrow to produce more white blood cells that help fight infection.

3. BEFORE YOU ARE ADMINISTERED ZARZIO:

Do not use ZARZIO:

- If you are allergic (hypersensitive) to filgrastim or any of the other ingredients of ZARZIO (see “WHAT ZARZIO CONTAINS”).
- If you are a patient with severe congenital neutropenia and you develop leukaemia (cancer of the blood) or are likely to develop leukaemia.
- If your child has cancer.
- If you have kidney and/or liver problems.
- If you are pregnant or breastfeeding your baby.
- If you are a stem cell donor and are not between the ages of 16 and 60 years (See “Take special care with ZARZIO”).

Take special care with ZARZIO:

Please tell your doctor immediately during treatment with ZARZIO, if you:

- Have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction (hypersensitivity).
- If your body’s defence system is already weakened, as ZARZIO may further weaken your body’s defence system (immune system).
- If you are intolerant to sorbitol, as ZARZIO contains sorbitol which may have a laxative effect.
- If you suffer from osteoporosis.
- If you have signs (e.g., cough, difficulty to breath, coughing up blood) of lung infections.
- Experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual (glomerulonephritis).
- Get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder (these may be symptoms of an enlarged spleen [splenomegaly], or possibly rupture of the spleen).
- Notice unusual bleeding or bruising (these may be symptoms of a decrease in blood platelets [thrombocytopenia], with a reduced ability of your blood to clot).
- Inflammation of aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever,

abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience those symptoms.

Pregnancy and breastfeeding:

You should not use ZARZIO if you are pregnant, planning to become pregnant or breastfeeding your baby.
If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or healthcare professional for advice before receiving ZARZIO.

Driving and using machinery:

ZARZIO may have an effect on your ability to drive and use machines. You may feel dizzy after receiving ZARZIO and it is advisable to wait and see how you feel after receiving ZARZIO before you drive or operate machines.

Important information about some of the ingredients of ZARZIO:

ZARZIO contains sorbitol (a type of sugar). If you have been told by your doctor that you have a reaction to some sugars, contact your doctor before taking this medicinal product.

Taking other medicines with ZARZIO:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)

- ZARZIO should not be used 24 hours before or after chemotherapy treatment.
- If you are taking medicine containing lithium, please inform your doctor.

4. HOW TO USE ZARZIO:

Do not share medicines prescribed for you with any other person.
Always use ZARZIO exactly as your doctor has told you. Check with your doctor, nurse or pharmacist if you are not sure.
ZARZIO is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an intravenous infusion). The

amount of ZARZIO you need depends on your body weight and the condition you are treated for. Your doctor will tell you how much ZARZIO you should take or receive.

You will need to take ZARZIO until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take ZARZIO.

Method of administration:

If you are receiving this medicine by subcutaneous injection, your doctor may suggest that you learn how to give yourself the injection. Your doctor or nurse will give you instructions on how to do this. Do not attempt to self-administer without this training. Some of the information you require is given at the end of this package leaflet, but proper treatment of your disease requires close and constant co-operation with your doctor.

If you forget to take/receive ZARZIO:

If you have missed an injection, contact your doctor as soon as possible to discuss when you should receive the next injection.

5. POSSIBLE SIDE EFFECTS:

ZARZIO can have side effects.

Not all side effects reported for ZARZIO are included in this leaflet.

Should your general health worsen or if you experience any untoward effects while taking/receiving this medicine, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking ZARZIO and tell your doctor immediately or go to the nearest casualty department at your nearest hospital:

- If you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face, lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea).

- If you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- If you experience kidney injury (glomerulonephritis). Symptoms are as follows; if you experience puffiness in your face or ankles, blood in your urine or brown-coloured urine or you notice you urinate less than usual.
- If you have any of the following or combination of the following side effects:
    - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion; these could be symptoms of a condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.
- If you have a combination of any of the following symptoms:
    - fever, or shivering, or feeling very cold, high heart rate, confusion or disorientation, shortness of breath, extreme pain or discomfort and clammy or sweaty skin; these could be symptoms of a condition called “sepsis” (also called "blood poisoning"), a severe infection with whole-body inflammatory response which can be life threatening and needs urgent medical attention.
- If you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your left shoulder, as there may be a problem with your spleen (enlargement of the spleen (splenomegaly) or rupture of the spleen).
- If you are being treated for severe chronic neutropenia and you have blood in your urine (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).

In patients undergoing a stem cell or bone marrow transplant, Graft versus host disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints.

In normal stem cell donors an increase in white blood cells (leukocytosis) and a decrease of platelets may be seen, this reduces the ability of your blood to clot (thrombocytopenia); these will be monitored by your doctor.

These are all serious side effects. You will need urgent medical attention.

Tell your doctor if you notice any of the following side effects that have been reported frequently:

- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- fever (pyrexia)
- inflammation of the lung (bronchitis)
- upper respiratory tract infection
- urinary tract infection
- decreased appetite
- trouble sleeping (insomnia)
- dizziness
- decreased feeling of sensitivity, especially in the skin (hypoesthesia)
- tingling or numbness of the hands or feet (paraesthesia)
- low blood pressure (hypotension)
- high blood pressure (hypertension)
- cough

- coughing up blood (haemoptysis)
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- constipation
- oral pain
- enlargement of the liver (hepatomegaly)
- rash
- redness of the skin (erythema)
- muscle spasm
- pain when passing urine (dysuria)
- chest pain
- pain
- generalised weakness (asthenia)
- generally feeling unwell (malaise)
- swelling in the hands and feet (oedema peripheral)
- increase of certain enzymes in the blood
- changes in blood chemistry
- transfusion reaction

Tell your doctor if you notice any of the following side effects that have been reported less frequently:

- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- high uric acid levels in the blood, which may cause gout (hyperuricaemia) (blood uric acid increased)
- liver damage caused by blocking of the small veins within the liver (veno-occlusive disease)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- inflammation of the lungs (interstitial lung disease)

- abnormal x-rays of the lungs (lung infiltration)
- bleeding from the lung (pulmonary haemorrhage)
- lack of absorption of oxygen in the lung (hypoxia)
- bumpy skin rash (rash maculo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- injection site reaction
- severe pain in the bones, chest, gut or joints (sickle cell anaemia with crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates fluids within your body and may result in puffiness (fluid volume disturbances)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- worsening of rheumatoid arthritis
- unusual change in the urine
- bone density decreased
- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

6. STORING AND DISPOSING OF ZARZIO:

- Store between 2 °C – 8 °C (in a refrigerator).
- Do not use ZARZIO after the expiry date which is stated on the syringe label and carton after EXP. The expiry date refers to the last day of that month.

- The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 72 hours (but not above 25 °C). At the end of this period, the product should not be put back in the refrigerator and should be disposed of.
- Keep the pre-filled syringe in the outer carton in order to protect from light.
- **STORE ALL MEDICINES OUT OF THE REACH OF CHILDREN.**
- Medicines should not be disposed of via wastewater or household waste.
- Any unused portion of ZARZIO should be discarded in accordance with local requirements**.**
- Return all unused medicines to your pharmacist.

7. PRESENTATION OF ZARZIO:

Primary packaging: Pre-filled colourless, transparent, 1 mL glass syringe containing 0,5 mL solution, with stainless steel injection needle, protected by a grey rubber formulation needle shield (guard) and with a grey flurotec coated bromobutyl plunger stopper.

Secondary packaging: Rigid polypropylene needle shield (cap) and polypropylene or polycarbonate plunger rod.

ZARZIO is available in packs containing 1, 3, 5 or 10 pre-filled syringes packed in a carton.

Not all pack sizes may be marketed.

8. IDENTIFICATION OF ZARZIO:

ZARZIO 30 MU: 1 mL long clear glass syringe with a grey stopper and stacked needle containing a colourless to slightly yellowish solution. Free from visible particulate matter.

ZARZIO 48 MU: 1 mL long clear glass syringe with a grey stopper and stacked needle containing a colourless to slightly yellowish solution. Free from visible particulate matter.

9. REGISTRATION NUMBERS:

ZARZIO 30 MU: 47/30.4/0603

ZARZIO 48 MU: 47/30.4/0604

10. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

11. DATE OF PUBLICATION:

Date of registration: 09 December 2019

Date of most recent approval of professional information: 09 December 2019

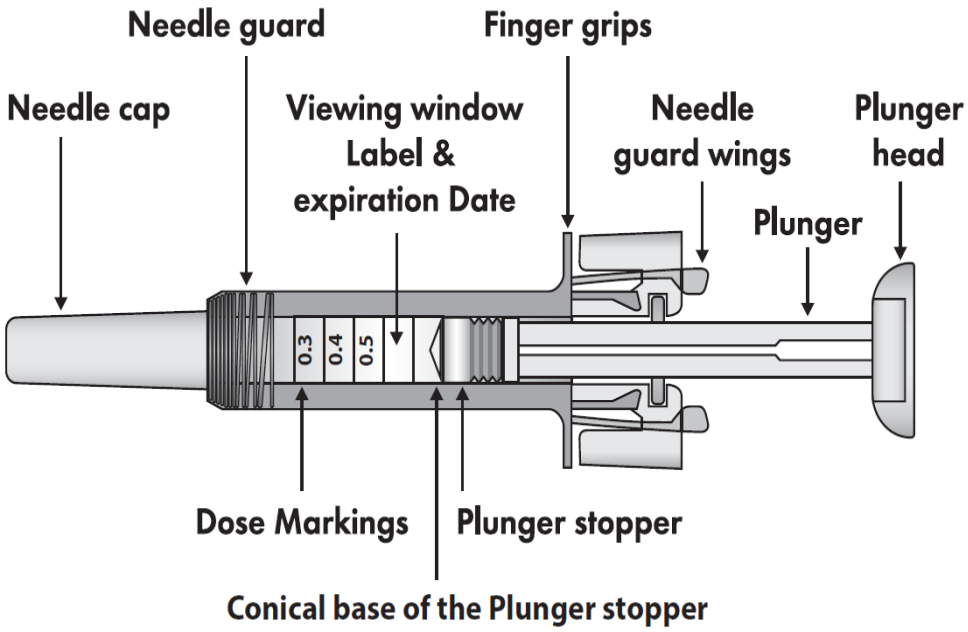
[1]Company Reg. No.: 1990/001979/07

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Instructions for injecting yourself with ZARZIO pre-filled syringe:

IMPORTANT: TO HELP AVOID A POSSIBLE INFECTION, YOU SHOULD FOLLOW THESE INSTRUCTIONS.

It is important not to try to inject yourself or someone else until you have been trained by your healthcare provider, nurse or pharmacist. Please read all the instructions before injecting. Each sealed blister contains one pre-filled syringe. Each pre-filled syringe contains 30 MU filgrastim per 0,5 mL or 48 MU filgrastim per 0,5 mL.

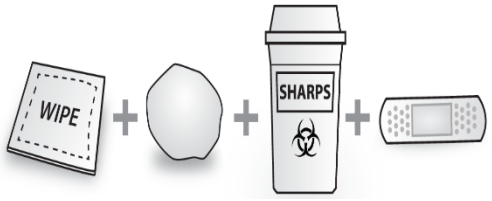


ZARZIO pre-filled syringe with needle guard

After the medication has been injected, the needle guard will be activated to cover the needle. This is intended to aid the protection of healthcare providers, patients who self-inject doctor-prescribed medicines and individuals who assist self-injecting patients from accidental needle-stick injuries.

What you additionally need for your injection:

- 1 Alcohol swab
- 1 Cotton ball or gauze.
- Sharps disposal container.
- 1 Adhesive bandage



Important safety information:

Caution: Keep the ZARZIO pre-filled syringe out of the reach of children.

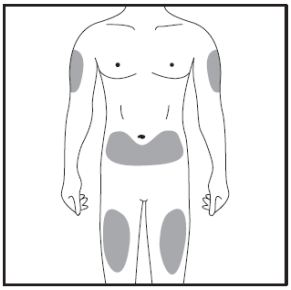
1. Do not open the outer box until you are ready to use the ZARZIO pre-filled syringe.
2. Do not use the ZARZIO pre-filled syringe if the seal of the blister is broken, as it may not be safe for you to use.
3. Never leave the ZARZIO pre-filled syringe unattended where others might tamper with it.
4. Avoid shaking the ZARZIO pre-filled syringe.
5. Be careful not to touch the needle guard wings before use. By touching them, the needle guard may be activated too early.
6. Do not remove the needle cap until just before you give the injection.
7. The ZARZIO pre-filled syringe cannot be re-used. Please dispose the used ZARZIO pre-filled syringe immediately after use in a sharps container.

Storage of the ZARZIO pre-filled syringe:

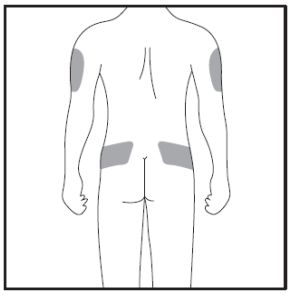
1. Store the ZARZIO pre-filled syringe in its outer carton box to protect it from light. Store it in a refrigerator between 2 °C and 8 °C. Protect from freezing. If frozen, thaw in the refrigerator before use. Throw away (dispose of) if it has been frozen more than 1 time.

2. Remember to take the ZARZIO blister out of the refrigerator and let it warm up for 15-30 minutes to allow it to reach room temperature before preparing it for the injection.
3. Do not use the ZARZIO pre-filled syringe after the expiration date shown on the outer box or syringe label. If it has expired, return the entire pack to the pharmacy.

The injection site:



The injection site is the place on the body where you are going to use the ZARZIO pre-filled syringe.
The recommended site is the front of your thighs. You may also use the lower abdomen, but **not** the area 5 cm (2 inches) around the navel (belly button).



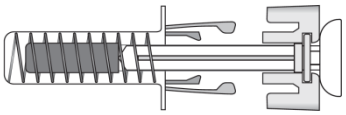
If a caregiver is giving you the injection, the outer upper arms and the upper areas of the buttocks may also be used.
Choose a different site each time you give yourself an injection.
Do not inject into areas where the skin is tender, bruised, red, scaly or hard. Avoid areas with scars or stretch marks.

Preparing the ZARZIO pre-filled syringe ready for use:

1. Take the blister containing the ZARZIO pre-filled syringe out of the refrigerator and leave it **unopened** for approximately 15-30 minutes, so that it can reach room temperature.
2. When you are ready to use the ZARZIO pre-filled syringe, open the blister and wash your hands thoroughly with soap and water.
3. Clean the injection site with an alcohol swab.
4. Remove the ZARZIO pre-filled syringe from the blister.

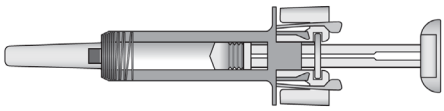
5. Check to ensure the plastic transparent needle guard is situated over the barrel of the glass syringe. If the transparent needle guard is covering the needle cap (as shown below Figure 1) the syringe has been activated, DO NOT use this syringe and take a new syringe. Figure 2 shows a ready to use syringe.

Figure 1 DO NOT USE



In this configuration the needle guard is ACTIVATED – DO NOT USE the pre-filled syringe

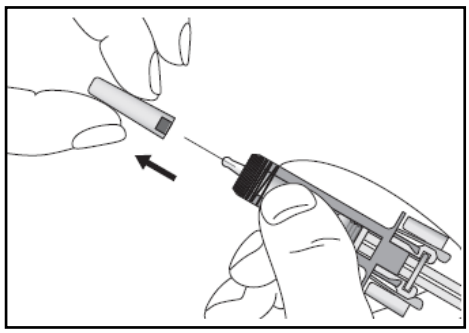
Figure 2 Ready to Use



In this configuration the needle guard is NOT ACTIVATED and the pre-filled syringe is ready for use

6. Inspect the ZARZIO pre-filled syringe. The solution should be clear, colourless to slightly yellowish and may contain small, translucent or white floating particles of protein. DO NOT USE if any other particulates and/or discolouration's are observed and return the pre-filled syringe and the package it came into the pharmacy.
7. DO NOT USE if the ZARZIO pre-filled syringe is broken or the needle guard activated. In all these instances, return the entire product pack to the pharmacy.

How to use the ZARZIO pre-filled syringe:



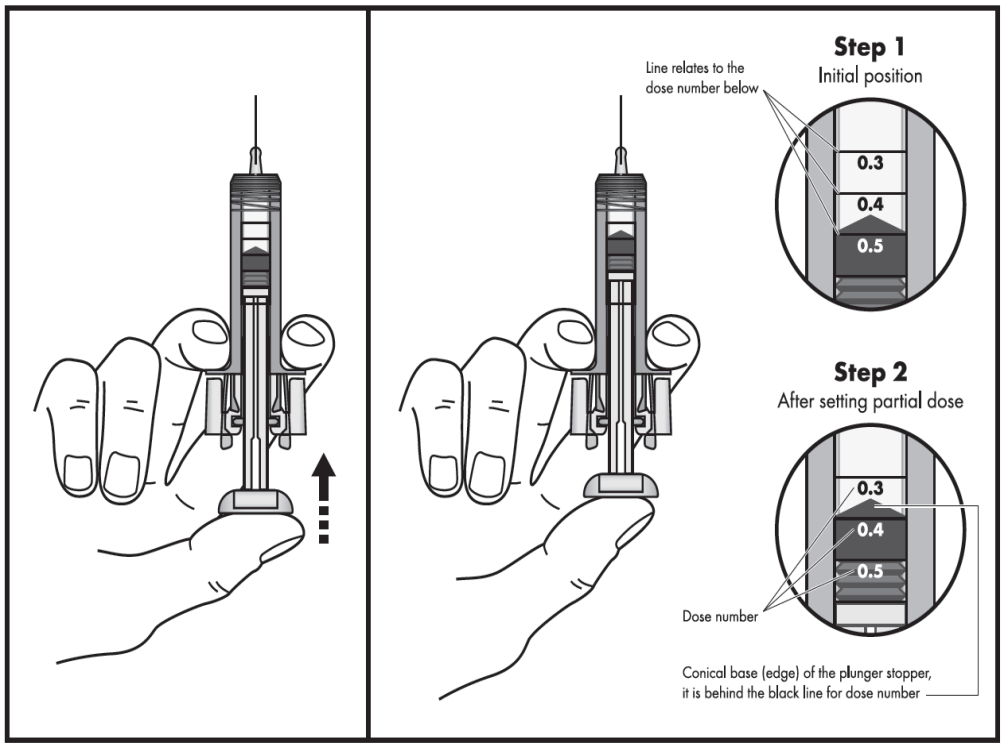
Carefully pull the needle cap straight off to remove it from the ZARZIO pre-filled syringe. Discard the needle cap. You may see a drop of liquid at the end of the needle. This is normal.

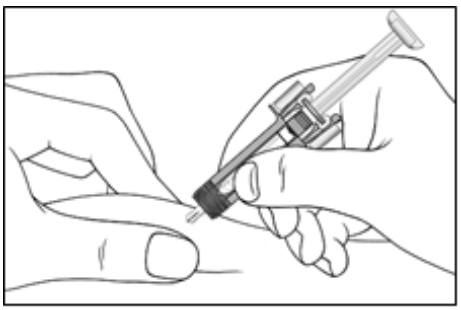
Holding the syringe as shown, press slowly on the plunger to push out the excess medicine until the edge of the conical base of the plunger stopper lines up with the syringe marking for your prescribed dose. Below example for a dose of 0,4 mL.

Be careful not to touch the needle guard wings before use. The needle guard may be activated too early.

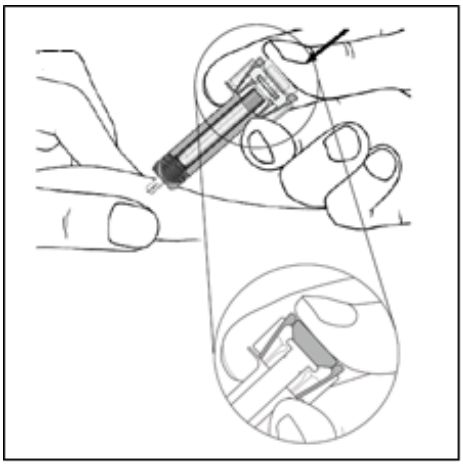
Check again to make sure the correct dose of ZARZIO is in the pre-filled syringe.

Call your healthcare provider or nurse if you have problems measuring or injecting your dose of ZARZIO.



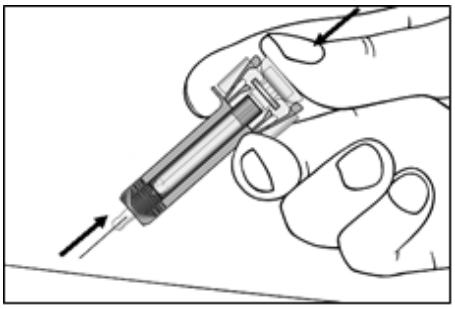


Gently pinch the skin at the injection site and insert the needle as shown. Push the needle all the way in to ensure that the medication can be fully administered.

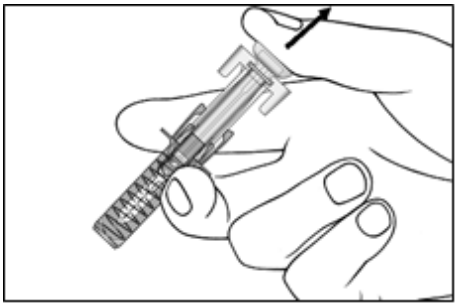


Holding the ZARZIO pre-filled syringe as shown, **slowly** depress the plunger **as far as it will go** so that the plunger head is completely between the needle guard wings.

Keep the plunger pressed fully down while you hold the syringe in place for 5 seconds.

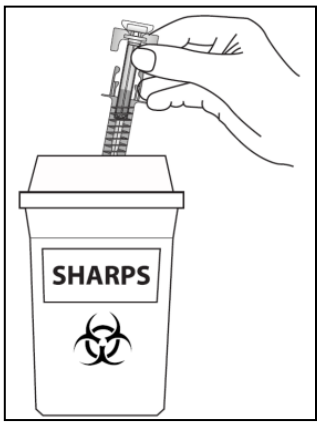


Keep the plunger fully depressed while you carefully pull the needle straight out from the injection site.



Slowly release the plunger and allow the needle guard to automatically cover the exposed needle.
There may be a small amount of blood at the injection site. You can press a cotton ball or gauze onto the injection site and hold it for 10 seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if needed.

Disposal instructions:



Dispose of the used syringe in a puncture-proof container (Sharps). For the safety and health of you and others, needles and used syringes must never be re-used.